University of Alberta

Oxonium Ylides in the Synthesis of Fused, Medium-Sized Rings

by

Graham Kevin Murphy ©

A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Chemistry

Edmonton, Alberta
Spring 2007

Library and Archives Canada

Published Heritage Branch

395 Wellington Street
Ottawa ON K1A 0N4
Canada

Bibliothèque et Archives Canada

Direction du Patrimoine de l'édition

395, rue Wellington
Ottawa ON K1A 0N4
Canada

Your file Votre référence
ISBN: 978-0-494-29718-6
Our file Notre référence
ISBN: 978-0-494-29718-6

NOTICE:
The author has granted a non-exclusive license allowing Library and Archives Canada to reproduce, publish, archive, preserve, conserve, communicate to the public by telecommunication or on the Internet, loan, distribute and sell theses worldwide, for commercial or non-commercial purposes, in microform, paper, electronic and/or any other formats.

The author retains copyright ownership and moral rights in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

AVIS:
L'auteur a accordé une licence non exclusive permettant à la Bibliothèque et Archives Canada de reproduire, publier, archiver, sauvegarder, conserver, transmettre au public par télécommunication ou par l'Internet, prêter, distribuer et vendre des thèses partout dans le monde, à des fins commerciales ou autres, sur support microforme, papier, électronique et/ou autres formats.

L'auteur conserve la propriété du droit d'auteur et des droits moraux qui protège cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

In compliance with the Canadian Privacy Act some supporting forms may have been removed from this thesis.

While these forms may be included in the document page count, their removal does not represent any loss of content from the thesis.

Conformément à la loi canadienne sur la protection de la vie privée, quelques formulaires secondaires ont été enlevés de cette thèse.

Bien que ces formulaires aient inclus dans la pagination, il n'y aura aucun contenu manquant.

Canada

I'm not afraid,
Of standing in the middle of this open space.
This sunny day,
Will step aside and make way for the comin rain.
Whatever's waitin I am ready so...

Wash the mountains away,
This is where I'll stay.
I'll be holdin strong and steady,
Cause I've spent way too long,
Runnin from the storm.
But not anymore, I am ready!!

I couldn't wait,
To stand and show the world that I had what it takes.
Tried not to break,
But I've learned that fallin down don't mean
You'll lose your way.
Whatever's waitin I am ready so...

Wash the mountains away,
This is where I'll stay.
I'll be holdin strong and steady,
Cause I've spent way too long,
Runnin from the storm.
But not anymore, I am ready!!

-Doc Walker

In Loving Memory of

Phillip Graham Murphy

10 / 10 / 1951 to 06 / 28 / 2005

Abstract

Oxonium ylides have found limited exposure in synthesis, mainly due to difficulties associated with their high reactivity. These putative intermediates are formed by capture of a diazoketone-derived metallocarbene by a pendant ethereal oxygen, and they have been shown to undergo synthetically useful rearrangements when appropriately substituted. Typically observed are the Stevens [1,2]-shift or the [2,3]-sigmatropic shift, which have been shown to give a wide variety of carbo- and heterocyclic structures in good yield, with high levels of chemoselectivity. Chapter 1 is a review of oxonium ylides in synthesis, emphasizing the factors that influence the subsequent reactivity of these intermediates.

The heteroatom-directed Stevens [1,2]-shift rearrangement protocol has been expanded to allow the synthesis of oxygen-bridged, fused 5-7 bicyclic ring systems in Chapter 2, wherein the products were recovered in good yield, with occasionally interesting chemoselectivity. Products resulting from rearrangements of oxonium ylides, and in some cases sulfonium ylides, were isolated. The occurrence of products from unanticipated rearrangements was dependant on the configuration of the starting diazoketone.

A novel method for the synthesis of oxonium ylides is described in Chapter 3, employing iodonium ylides as diazoketone surrogates for generating metallocarbene intermediates. This protocol was found to be catalyst-dependant, and to afford the products in equal, and in some cases greater yield, than the corresponding diazoketone

processes in the aliphatic series investigated. The diazoketone protocol was found to be more effective than the iodonium ylide-mediated method for the aromatic substrate tested.

Finally, the application of the sulfur-directed Stevens [1,2]-shift was employed in the attempted total synthesis of the natural product (+)-dactylol in Chapter 4. Several variations on the original synthetic scheme were also examined, due to the occurrence of undesired transannular processes late in the synthetic sequence. Initially, we rearranged the order of the overall sequence to decrease the likelihood of such transannular reactions from occurring, but this was found to be unworkable. Lastly, an entirely new method for preparing the diazoketone precursor was developed. This precursor is designed to potentially enable the synthesis of (+)-dactylol by either the original sulfur-directed Stevens [1,2]-shift, or by a [2,3]-sigmatropic rearrangement.

Acknowledgement

First and foremost, I would like to thank my boss and friend, Dr. Fred West. It has been a pleasure to spend the last five years learning from you. Whether the topic was chemistry or other lessons that you felt I needed to learn, you appear to have gotten the point across. I know that I have grown by leaps and bounds as a chemist and otherwise, and I feel that this was largely due to your example. I am sorry for all the headaches over the years, really.

I would like to extend my gratitude to the members of the West group. These past five years have come and gone so quickly, and it has been a pleasure to share them with you. First of all, I would like to thank former member Dr. Fred Marmsäter. He introduced me to the world of carbenes, and showed me what it takes to get the job done. I am fully aware that without his help at the outset of this degree, I would not yet be close to finished. For this I am grateful. I would also like to thank Chantel, Nina, Dong, Tina and Hayley who were there in the early years of the group. Be it 502 or candidacy preparation, or just getting downright silly in the lab, you were there, and I thank you. I would also like to thank a number of the later group members including Craig, Damian, Lei, Karl, Liya, Curtis and Tina. It has been fun.

To those who have made this degree more of an adventure, I say thank you. Skiing with J.R. & Sarah, Kwinberg, 6-Wing or Boudreau, was always a hell of a time. I have enjoyed playing numerous sports with too many to mention, so here's to the Frogs, Lions and an Eagle, as well as the softball team (in whatever the current incarnation might be). To the squash partners, thank you. I can't forget to acknowledge those with whom I shared laughs, so here's a try: J.R., Meethal, T-Granny, Benny, 6-Wing, Kwinberg, Sir Todd, Hippie, Tbott, J.C., The Boss, Scotty-Mac, Boudreau and all the rest…

Lastly, I need to thank my family. Pam (Marge), Phil (Mr. Phil), Adam (Murph) & Kara, Aron (Remington) and Gil, thank you. I have spent more than twelve years

getting this degree, and I know that it would not have happened without the love and support of all of you. There were some wonderful highs and some terribly unfortunate lows, and together we experienced them all. Without all of you I would probably have ended up behind bars, as was predicted, so thank you for setting me straight. To Melissa, what can I say? Oh, wait, I already did…

Table of Contents

1. CHAPTER 1 1

1.1. Introduction 1

1.2. Background 1

1.3. Synthesis Employing Monocyclic Oxonium Ylides 8

1.3.1. Preliminary Investigatons 8

1.3.2. The [2,3]-Sigmatropic Rearrangement 10

1.3.3. The Stevens [1,2]-Shift 11

1.3.4. The Synthesis of (+)-Griseofulvin 12

1.3.5. The Value of n: Oxonium Ylide Ring Size 13

1.3.6. The Effect of Catalyst 15

1.3.7. The Induction of Asymmetry in Rearrangements of Oxonium Ylides 18

1.4. The Mechanism of Ylide Formation and Rearrangement 19

1.4.1. Primary Considerations 19

1.4.2. Ylide Reversibility 19

1.4.3. The Mechanism of the [2,3]-Sigmatropic Rearrangement 22

1.4.4. The Mechanism of the Stevens [1,2]-Shift 23

1.4.5. [1,2]- vs [1,4]- Shifts 26

1.4.6. Evidence that the Copper and Rhodium Mechanisms are Different 28

1.4.7. Selected Applications in Synthesis 30

1.5. The Synthesis of Bicyclic Oxonium Ylides 35

1.5.1. THP and THF Derived Oxonium Ylides 35

1.5.2. Oxonium Ylides Generated from Ketals 40

1.5.3. Oxonium Ylides for Ring Expansion 46

1.6. Conclusions 51

1.6. References 54

2. CHAPTER 2 61

2.1. Introduction 61

2.2. Background 63

2.3. Results and Discussion 64

2.3.1. The initial investigation. 64

2.3.2. The oxygen-stabilized [1,2]-shift in the synthesis of a fused 5-8 bicycle. 67

2.3.3. The Mechanism of the Stevens [1,2]-shift. 68

2.3.4. Toward the synthesis of the fused 5-5 diazoketones 69

2.3.5. Developing a new protocol for diazoacylation 71

2.3.6. The synthesis of the fused 5-7 bicycles: Determining the structure of the products. 73

2.3.7. The oxygen and sulfur-stabilized Stevens [1,2]-shift. 77

2.3.8. The synthesis and rearrangement of b-keto ester substrates. 79

2.3.9. Cleavage of the bridging ether 82

2.4. Conclusions and Future Work 83

2.5. Experimental 84

2.5.1. General 84

2.5.2. Substrate Syntheses 85

2.6. References 105

3. CHAPTER 3 110

3.1. Introduction 110

3.2. Background 111

3.3. Results and Discussion 115

3.3.1. Synthesis and rearrangement of the diazo substrates. 115

3.3.2. The iodonium ylide mediated shifts 117

3.3.3. The iodonium ylide-mediated rearrangement of an aromatic substrate 121

3.3.4. Asymmetric induction in the iodonium ylide-mediated [2,3]-shift. 121

3.4. Conclusions and Future Work 122

3.5. Experimental 124

3.5.1. General 124

3.5.2. Substrate Syntheses 125

3.6. References 134

4. CHAPTER 4 141

4.1. Introduction 141

4.2. Background 141

4.2.1. Biosynthesis 141

4.2.2. The Hayasaka Synthesis of Dactylol 143

4.2.3. The Paquette Synthesis of Dactylol 144

4.2.4. The Gadwood Syntheses of Dactylol 145

4.2.5. The Feldman Synthesis of (+)-Dactylol 148

4.2.6. The Molander Synthesis of (+)-Dactylol 150

4.2.7. The Fürstner Synthesis of Dactylol 153

4.2.8. The Harmata Synthesis of (+)-Dactylol 154

4.3. Results and Discussion 156

4.3.1. Preliminary Considerations 156

4.3.2. The Retrosynthesis 157

4.3.3. The First Generation Synthesis of (+)-Dactylol 158

4.3.4. The Second Generation Synthesis of (+)-Dactylol 163

4.3.5. The Third Generation Synthesis of (+)-Dactylol 166

4.4. Conclusions and Future Work 176

4.5. Experimental 178

4.5.1. General 178

4.5.2. Substrate Syntheses 179

4.6. References 202

Appendix Chapter 2 211

Appendix Chapter 3 227

Appendix Chapter 4 230

List of Tables

Table 3.1: The diazoketone-mediated [1,2]- and [2,3]-shifts of oxonium and sulfonium ylides. 116

Table 3.2: The iodonium ylide-mediated [1,2]- and [2,3]-shifts of oxonium and sulfonium ylides. 119

List of Figures

Figure 1.1: Structure of an oxonium ylide.....1
Figure 1.2: Metallocarbene reactive pathways. 3
Figure 1.3: [1,2]-Rearrangements of oxonium ylides generated indirectly from trialkyloxonium ions. 3
Figure 1.4: Onium ylide formation upon carbene transfer. 4
Figure 1.5: Possible reactive pathways upon formation of an oxonium ylide.....6
Figure 1.6: Endocyclic and exocyclic migrating group connectivities of oxonium ylides.6
Figure 1.7: C-H insertion competes with formation of >5-membered ylides.....7
Figure 1.8: Structural factors that impact the outcome of oxonium ylide processes. 8
Figure 1.9: The modes of rearrangement for the allylic shift. 11
Figure 1.10: The proposed mechanisms for the [2,3]-sigmatropic rearrangement. 23
Figure 1.11: The transition metal-free [1,2]-shift mechanism. 24
Figure 1.12: The benzyl transfer / reductive elimination proposal for [1,2]-shift 25
Figure 1.13: The metal-assisted homolysis / recombination proposal for the [1,2]-shift.26
Figure 1.14: The reactive pathways typically undergone by bicyclic oxonium ylides. ...35
Figure 1.15: The mechanism of the Oku Process.....47
Figure 1.16: The reactive pathway of an oxygen-assisted ring opening. 48
Figure 1.17: The ortho ester substrates tested by Oku, as well as the carbomethoxy-substituted substrates to provide anion stabilization. 50
Figure 2.1: Examples of fused 5-7 and 5-8 bicycles with bridgehead oxygenation. 62
Figure 2.2: Substrates for heteroatom-stabilized exocyclic [1,2]-shifts, by analogy.....63
Figure 2.3: Possible variations in the synthesis of oxygen-bridged, fused carbocycles by the heteroatom-stabilized Stevens [1,2]-shift.....64
Figure 2.4: The mechanism of the [1,2]-shift, with emphasis on diastereo-selectivity. ..69
Figure 2.5: G.C. analysis of the reaction mixtures from the transition metal-catalyzed decomposition of 32α (Peaks 1-4). Analysis of the product mixtures after column chromatography (Peaks 1,3 and 2,4). 74
Figure 2.6: Structures of the products from the Stevens [1,2]-shift of 31α.....75

Figure 2.7: MM2 minimized 3D representation of the intermediate metallocarbene of the α-anomer. 76
Figure 2.8: The proposed mechanism for the formation of 33α,β. 76
Figure 2.9: Relative area % for the products observed from the catalyst survey in the [1,2]-shift of **31α**. 77
Figure 2.10: MM2 minimized 3D representation of the intermediate metallocarbene of the β-anomer. 78
Figure 3.1: Structures of common I^{V} and I^{III} oxidizing agents IBX, DMP, DAIB and DTFAIB. 111
Figure 3.2: Reactions common to the I^{III} oxidizing agents. 112
Figure 3.3: The reaction sequence of diazo- or iodonium ylide-mediated carbenoid processes. 113
Figure 4.1: Structures of natural products biosynthetically-derived from humulene **2**. 142
Figure 4.2: Proposed mechanism of the biosynthesis of (+)-dactylol from humulene. 142
Figure 4.3: The retrosynthetic analysis of (+)-dactylol. 158
Figure 4.4: Incorporating the geminal dimethyl groups via cyclopropanation / hydrogenolysis. 166
Figure 4.5: The transesterification / Carroll rearrangement sequence. 168

List of Schemes

Scheme 1.1: Early examples of oxonium ylide rearrangements from metallocarbenes.....5
Scheme 1.2: The ylide formation / fragmentation sequence of Zwanenburg.....8
Scheme 1.3: Selected exocyclic [2,3]-shifts of Pirrung and Johnson. 9
Scheme 1.4: Endocyclic [1,2]-shift, [2,3]-shift and fragmentation reactions observed by Johnson.[21] 10
Scheme 1.5: The [1,2]-shift of an electron deficient migrating group. 12
Scheme 1.6: The synthesis of (+)-griseofulvin. 13
Scheme 1.7: 5-Membered vs 6-membered oxonium ylide formation in the aliphatic allyl [2,3]-shift.....13
Scheme 1.8: 5-Membered vs 6-membered oxonium ylide formation in the aromatic allyl [2,3]-shift.....14
Scheme 1.9: 5-Membered vs 6-membered oxonium ylide formation in the aliphatic benzyl [1,2]-shift. 14
Scheme 1.10: Competitive 5-membered vs 6-membered oxonium ylide formation in the aliphatic benzyl [1,2]-shift. 15
Scheme 1.11: Comparison of fluorinated vs non-fluorinated ligands in the rhodium-catalyzed intermolecular [2,3]-shift.....16
Scheme 1.12: Copper catalysts effective in promoting the [2,3]-shift in systems of increasing ring size. 17
Scheme 1.13: The first use of chiral ligands in transition metal-catalyzed oxonium ylide processes. 19
Scheme 1.14: Model study to determine the outcome of methyl-substituted oxonium ylide formation. The product observed is from a [1,4]-shift.....20
Scheme 1.15: C-H insertion products isolated from carbene transfer on 50. Ylide reversibility is proposed to account for the observation of 51 and 52.....21
Scheme 1.16: Competition study between 5-membered benzyl [1,2]- and 6-membered allyl [2,3]-shifts. Ylide reversibility is proposed to account for the formation of 55. 22

Scheme 1.17: Homodimeric products recovered by West and co-workers during a benzyl [1,2]-shift.....23
Scheme 1.18: [1,4]-Shift products isolated from [1,2]-shift processes. 27
Scheme 1.19: Promoting for [1,4]-shift products through variably-substituted benzyl [1,2]-shifts. 28
Scheme 1.20: Differing product distributions for Rh and Cu catalysts.....29
Scheme 1.21: [1,2]-Shift vs [2,3]-shift competition study using Rh and Cu catalysts. ...29
Scheme 1.22: The racemic and enantioselective syntheses of (±)-decarestrictine L.....30
Scheme 1.23: Synthesis of the A-ring of the gambieric acids. 31
Scheme 1.24: Iterative approach to the polypyran motif.....32
Scheme 1.25: Conformational analysis of endocyclic [2,3]-shifts.....33
Scheme 1.26: A tandem endocyclic [2,3]-shift / Diels-Alder cycloaddition.....33
Scheme 1.27: An endocyclic [2,3]-shift to afford a bicyclo[6.4.0]dodecane skeleton. ...34
Scheme 1.28: Tandem intramolecular ene-yne metathesis / [2,3]-rearrangement.....34
Scheme 1.29: The exocyclic benzyl [1,2]-shift of diazoketone-substituted THFs. 36
Scheme 1.30: The exocyclic benzyl [1,2]-shift of diazoketone-substituted THPs. 37
Scheme 1.31: Acetal-derived oxygen-bridged heterocycles.....38
Scheme 1.32: Ring expansion through [2,3]-shift of a vinyl-substituted THF.....38
Scheme 1.33: Model study and the synthesis of the core of neoliacinic acid.....39
Scheme 1.34: Synthesis towards the core of litophynin E and I.....40
Scheme 1.35: Synthesis towards the core of labiatin A. 40
Scheme 1.36: Rearrangement and fragmentation pathways of a bicyclic oxonium ylide. 41
Scheme 1.37: The endocyclic [1,2]-shift of an unsubstituted dioxolane.....42
Scheme 1.38: The attempted [1,2]-shift of a diethyl-substituted dioxolane.....42
Scheme 1.39: The vinyl-stabilized exocyclic [1,2]-shift.....43
Scheme 1.40: The benzyl-stabilized exocyclic [1,2]-shift.....44
Scheme 1.41: The endocyclic [1,2]-shift of an unsubstituted dioxane.....44
Scheme 1.42: Competition study between the endo- and exocyclic [1,2]-shifts of a ketal-derived oxonium ylide. 45
Scheme 1.43: Towards the core of zaragozic acid. 46

Scheme 1.44: The ring expansion of a bicyclic oxonium ylide. 46
Scheme 1.45: Ring expansion of dioxolane-derived oxonium ylides. 49
Scheme 1.46: The oxonium ylide / aldol trapping reaction. 51
Scheme 2.1: Preparation of the Stevens rearrangement precursor 65
Scheme 2.2: The Stevens [1,2]-shift of a sulfur-stabilized anomeric carbon. 66
Scheme 2.3: Sulfur mediated cleavage of the bridging ether in the 5-8 bicycle 66
Scheme 2.4: The Stevens [1,2]-shift of an oxygen-stabilized anomeric carbon. 68
Scheme 2.5: Synthesis of the mixed acetal and mixed thioacetal diazoketone precursors. 71
Scheme 2.6: Synthesis of the mixed acetal and mixed thioacetal diazoketones. 72
Scheme 2.7: Synthesis of the diazoketone precursors for the synthesis of fused 5-7 bicycles 73
Scheme 2.8: The Stevens [1,2]-shift of a sulfur-stabilized anomeric carbon. 78
Scheme 2.9: The Stevens [1,2]-shift of an oxygen-stabilized anomeric carbon. 79
Scheme 2.10: Synthesis of the di-stabilized α-diazo-β-keto ester substrates. 80
Scheme 2.11: The Stevens [1,2]-shift of a sulfur-stabilized anomeric carbon from a di-stabilized oxonium ylide. 81
Scheme 2.12: Scheme 12: Sulfur mediated cleavage of the bridging ether in the 5-7 bicycle. 83
Scheme 3.1: Early reports of carbenoid processes from iodonium ylides 112
Scheme 3.2: Synthesis of the substrates to undergo iodonium ylide-mediated (**2a-d**) and diazoketone-mediated (**3a-d**) carbene transfer and rearrangement. 115
Scheme 3.3: Stable sulfonium ylides isolated from carbene reactions. 117
Scheme 3.4: The diazoketone- and iodonium ylide-mediated [2,3]-shift of an aromatic allyl ether substrate. 121
Scheme 3.5: Asymmetric induction using chiral rhodium carboxylate catalysts. 122
Scheme 4.1: The synthesis of dactylol **1** from africanol **5** 143
Scheme 4.2: The Paquette synthesis of dactylol, part 1. 144
Scheme 4.3: The Paquette synthesis of dactylol, part 2. 145
Scheme 4.4: Gadwood synthesis of (+)-dactylol **1** from poitediol **3** 146

Scheme 4.5: Representative example of the divinyl cyclobutanol anionic oxy-Cope rearrangement from Gadwood.....146
Scheme 4.6: The second Gadwood synthesis of dactylol, part 1.....147
Scheme 4.7: The second Gadwood synthesis of dactylol, part 1.....148
Scheme 4.8: Representative example of the tropone-alkene [6π+2π] photocycloaddition. 149
Scheme 4.9: The Feldman synthesis of dactylol.....150
Scheme 4.10: The annulation protocol developed by Molander for the synthesis medium-sized rings.....151
Scheme 4.11: The Molander synthesis of (+)-dactylol. 152
Scheme 4.12: The model study by Molander for the cleavage of a bridging ether. 153
Scheme 4.13: The Furstner synthesis of dactylol.....154
Scheme 4.14: Representative examples of the intramolecular [4+3] cycloaddition.....155
Scheme 4.15: The Harmata synthesis of (+)-dactylol, part 1. 155
Scheme 4.16: The Harmata total sunthesis of (+)-dactylol. 156
Scheme 4.17: Toward the synthesis of (+)-dactylol, beginning with (+)-Pulegone. 159
Scheme 4.18: Mixed thioacetal formation and ester saponification. 160
Scheme 4.19: The Stevens [1,2]-shift and the reductive desulfurization. 161
Scheme 4.20: Oxidation with allylic inversion: transannular hemi-ketal formation. 161
Scheme 4.21: Attempts at protecting the alcohols as acetate or acetal. 162
Scheme 4.22: Attempts to protect the bridgehead alcohol. 163
Scheme 4.23: Dimethyl acetal formation in the presence of a ketone was ineffective..164
Scheme 4.24: Dithioacetal formation in the presence of a ketone was effective.....165
Scheme 4.25: Prenyltributyltin addition into enone 60. 165
Scheme 4.26: Alkylation of **52** with bromomethyl ethyl acrylate. 167
Scheme 4.27: Synthesis of the Carroll rearrangement substrate by transesterification. 169
Scheme 4.28: Synthesis of the β-keto acid **119**. 170
Scheme 4.29: Esterification of acid **119** proves unsuccessful with alcohol **115**. 170
Scheme 4.30: Preparation of the silyl-protected alcohols for use as alternative coupling partners.....171
Scheme 4.31: The palladium-catalyzed decarboxylative allylation.....172

Scheme 4.32: Attempted cyclopropanation of a diethylacetal **109**. 173
Scheme 4.33: Reformatsky addition, followed by attempted cyclopropanation on **109**. 174
Scheme 4.34: The attempted cyclopropanation on alcohol **133** and diol **134**. 174
Scheme 4.35: Attempted cyclopropanation on the allylic diol failed. 175
Scheme 4.36: Closing the ether by alkylation. A new approach to (+)-dactylol. 176
Scheme 4.37: Final strategy in the sulfur-stabilized Stevens [1,2]-shift mediated synthesis. 177
Scheme 4.38: The synthesis of (+)-dactylol via a [2,3]-sigmatropic rearrangement. 178

List of Abbreviations

Ac	acetyl
acac	acetylacetonate
Ar	aryl
app	apparent (spectral)
BORSM	based on recovered starting material
Bn	benzyl
br	broad (spectral)
i-Bu	*iso*-butyl
n-Bu	butyl
t-Bu	*tert*-butyl
°C	degrees Celsius
calcd	calculated
corr	correlation
COSY	homonuclear correlation spectroscopy
CSA	(1R)-(-)-camphorsulfonic acid
Cy	cyclohexyl
d	day(s); doublet (spectral)
DABCO	1,4-diazabicyclo[2.2.2]octane
DAIB	bis(acetoxy)iodobenzene
DBB	4,4'-di-*tert*-butylbiphenyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
dd	doublet of doublets (spectral)
Dibal-H	diisobutylaluminum hydride
DMAP	4-*N*,*N*-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide

dr	diastereomeric ratio
DTFAIB	bis(trifluoroacetoxy)iodobenzene
ee	enantiomeric excess
EI	electron impact (mass spectrometry)
equiv	equivalents
eq.	equation
ESY	electrospray ionization (mass spectrometry)
EtOAc	ethyl acetate
g	gram(s)
G	migrating group
G.C.	gas chromatography
h	hour(s)
hfacac	hexafluoroacetylacetonate
HMBC	heteronuclear multiple bond coherence
HMQC	heteronuclear multiple quantum coherence
hv	light
HRMS	high resolution mass spectrum
Hz	hertz
IBX	*o*-Iodoxybenzoic acid
J	coupling constant (in NMR)
L	liter(s)
LiDBB	lithium 4,4'-di-*tert*-butylbiphenylide
M	moles per liter
m	multiplet (spectral)
m-CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
MHz	megahertz
min.	minute(s)
mM	millimoles per liter
mol	mole(s)
m.p.	melting point

m/z	mass to charge ratio (in mass spectrometry)
nm	nanometers (light)
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
Nu	nucleophile
PCC	pyridinium chloroformate
pfb	perfluorobutyrate
Ph	phenyl
piv	pivaloyl
PMB	*p*-methoxybenzyl
ppm	parts per million (in NMR)
pyr	pyridine
q	quartet (spectral)
RaNi	Raney nickel
R_f	retention factor (in chromatography)
R_t	retention time (in gas chromatography)
r.t.	room temperature
s	singlet (NMR); second(s)
t	triplet (spectral)
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TBSOTf	*tert*-butyldimethylsilyl triflate
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetate
tfacac	trifluoroacetylacetonate
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
T.M.	transition metal

TMS	trimethylsilyl
Tol	tolyl
tpa	triphenylacetyl
TPAP	tetra-*n*-propylammonium perruthenate
Ts	tosyl; *p*-toluenesulfonyl
p-TsOH	*p*-toluenesulfonic acid

1. Chapter 1

Oxonium Ylides in Synthesis

1.1. Introduction

An ylide is a neutral molecule with opposing charges on adjacent atoms. Oxonium ylides are putative reactive intermediates whose existence has yet to be proven spectroscopically (Figure 1.1).[1,2] Evidence for their existence comes from the fact that substrates whose reactivities are known to include other onium ylides afford analogous products when oxygen-substituted. While onium ylides of nitrogen, phosphorus or sulfur are most easily generated indirectly through deprotonation of an onium ion, this is not effective for oxonium ylides. As powerful alkylating agents, oxonium ions are prone to donate an alkyl group rather than succumb to deprotonation, and as such their use in synthesis has been limited. The most practical entry into the formation of oxonium ylides comes from the transition metal-catalyzed diazoketone decomposition to afford a metallocarbene, which can undergo attack by a lone pair of electrons from an ether oxygen. This process, and the subsequent chemistry of the resulting ylides will be the focus of this chapter.

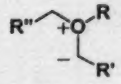


Figure 1.1: Structure of an oxonium ylide.

1.2. Background

Metallocarbenes derived from diazoketones are highly versatile reactive intermediates that have a variety of associated reactive pathways. Upon diazo decomposition by various means (irradiation, thermolysis or treatment with a transition metal catalyst) highly reactive intermediary carbenes are formed. By controlling solvent, temperature, catalyst used as well as intelligent substrate design, these high-energy intermediates can be made to react quite specifically to provide products not readily available through other reactive pathways. It is these factors that make diazoketones valuable synthetic precursors.

The first known example of the use of diazoketones in synthesis was in 1912 when Wolff discovered the diazoketone rearrangement that bears his name.[3] Diazoketones decompose to afford "free" carbenes upon thermolysis or irradiation with light. Treatment of diazoketones with a transition metal (typically rhodium or copper) results in carbene transfer, and irreversibly makes a transient metallocarbene of increased stability over the "free" carbenes. These metallocarbenes have shown moderate reactivity in various carbenoid pathways (Figure 1.2):

1. C-H or X-H insertion, where X could be N, O, S, Se, P
2. Dimerization
3. Cyclopropanation
4. Ylide formation

The first three of these processes are well known, and have been extensively documented in the literature.[4] However, ylide formation, especially oxonium ylide formation, is less well established.

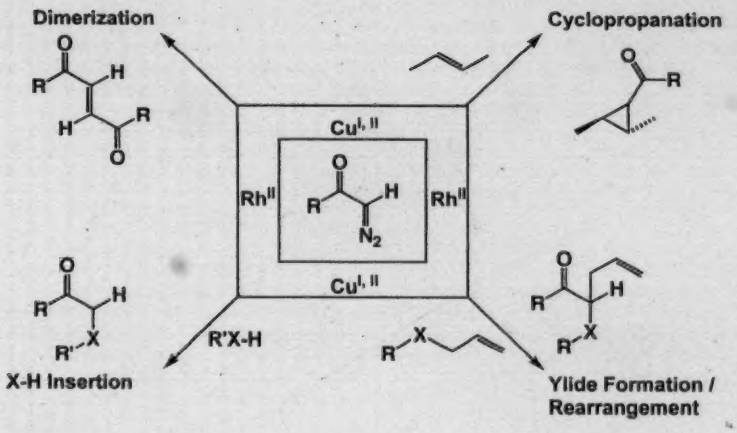


Figure 1.2: Metallocarbene reactive pathways.

Atoms that are more Lewis basic are more likely to undergo ylide formation. Isolable ylides of the elements nitrogen, sulfur and phosphorus can all be prepared indirectly by deprotonating α- to an onium ion.[5] There are, however, relatively few examples of oxonium ylides formed by indirect means and, as such, these have found much less exposure in chemical synthesis. One example involves the α-deprotonation or α-desilylation of an oxonium ion (Figure 1.3).[6-8] These indirect methods suffer from the observation that oxonium ions are powerful alkylating agents, and react preferentially as electrophiles rather than Brønsted acids. The competitive side processes of the indirect generation methods result in non-specific reactions of limited synthetic scope.

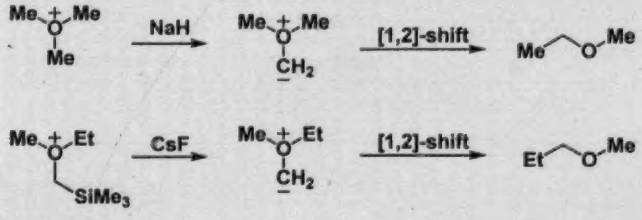


Figure 1.3: [1,2]-Rearrangements of oxonium ylides generated indirectly from trialkyloxonium ions.

Atoms that readily make ylides by indirect means are also those that can make stable ylides most easily by direct transition metal-mediated carbene transfer. Ylide formation arises when a heteroatom possessing a Lewis basic lone pair of electrons is able to attack or intercept the electron-deficient metallocarbene, thus imparting a negative charge on the metallocarbene carbon (or transition metal) and a positive charge upon itself (Figure 1.4).

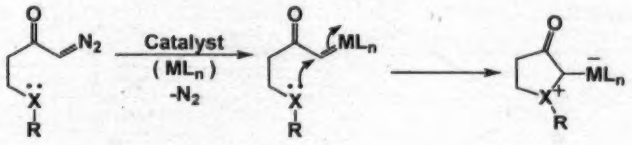
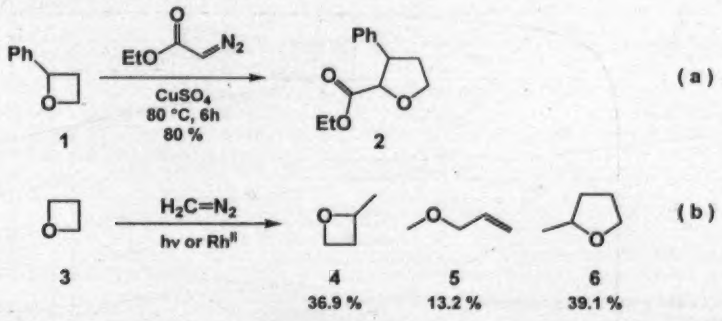


Figure 1.4: Onium ylide formation upon carbene transfer.

Two classes of oxygen-based ylides can result from the transition metal-mediated decomposition of diazoketones: oxonium ylides, which are the result of an ethereal oxygen intercepting a metallocarbene, and carbonyl ylides, which result from a carbonyl oxygen intercepting a metallocarbene. There are many examples of carbonyl ylides in chemical synthesis, particularly in the area of [3+2] dipolar cycloadditions, but they will not be discussed here.[9,10] The formation of oxonium ylides and the chemistry of these ylides will be the focus of this review. The development of mild catalytic methods for the generation of oxonium ylides has resulted in adoption of these methods more frequently in synthesis. Though the exact nature of oxonium ylides is still unknown, as is the mechanism of any subsequent reactivity, it is easiest to view them as ylides with reaction profiles similar to ylides of N, P and S.

Preliminary investigations in this area by Nozaki[11,12] concerned the intermolecular reaction of ethyl diazoacetate with 2-phenyloxetane. In these studies he observed the products of oxonium ylide formation and subsequent [1,2]-shift of the phenyl-substituted carbon (Scheme 1.1, eq. a). Subsequent to this, Kirmse investigated the photochemical (and the rhodium-catalyzed) decomposition of diazomethane in the presence of 2-methyloxetane. The expected C-H insertion (**4**) and fragmentation (**5**) products were

observed with the product of oxonium ylide formation, followed by a [1,2]-rearrangement (**6**) (Scheme 1.1, eq. b).[13, 14] These examples demonstrate two of the possible rearrangement processes available to oxonium ylides.



Scheme 1.1: Early examples of oxonium ylide rearrangements from metallocarbenes.

The intramolecular formation of oxonium ylides has proven the most synthetically viable, minimizing competition by alternative carbenoid pathways. However, even with intramolecular formation of an oxonium ylide, there are still numerous competing reactive pathways (Figure 1.5). These include:

1. Rearrangements: The Stevens [1,2]-shift and the [2,3]-shift.
2. α'-β Fragmentation: A proton-transfer / fragmentation sequence.
3. Nucleophilic trapping: A protonation / nucleophilic trapping sequence.

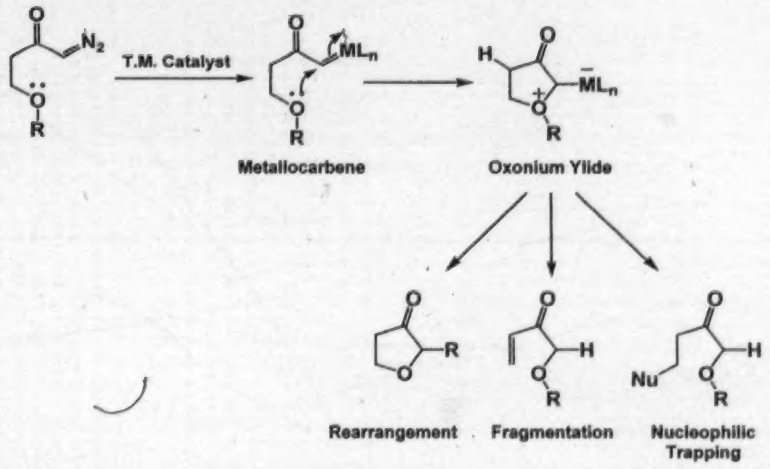


Figure 1.5: Possible reactive pathways upon formation of an oxonium ylide.

Given the high reactivity of oxonium ylides, a combination of informed substrate design and use of appropriate reaction conditions is required to favor the desired pathway and minimize competing processes. The intramolecular generation of an oxonium ylide creates a heterocyclic ring, thus one classification that can be made about substrates undergoing rearrangement is whether this will be an endocyclic or exocyclic process (Figure 1.6). This is defined by whether or not the migrating group (G) is fused within the carbocyclic framework (endocyclic) or outside the carbocyclic framework (exocyclic).

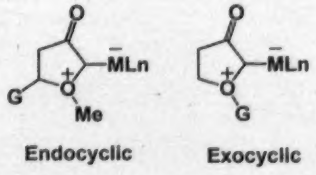


Figure 1.6: Endocyclic and exocyclic migrating group connectivities of oxonium ylides.

The nature of the migrating group (G) will determine whether the rearrangement will be a [1,2]-shift or a [2,3]-rearrangement. There are several factors that can affect the subsequent rearrangement with respect to yield, chemoselectivity and

diastereoselectivity. When substituted with an inappropriate migrating group, products of alternative metallocarbene processes are obtained, most commonly C-H insertion in bonds α- to ether oxygens.[15, 16]

It has been noted that C-H insertion reactions which proceed via metallocarbenes show a kinetic preference for the formation of five-membered rings.[17,18] Thus, for a value of $n = 1$, one would expect the onium ylide pathway to be a dominant process upon carbene transfer. For values of n greater than 1, competing reactive pathways would be expected, most typically C-H insertion (Figure 1.7).

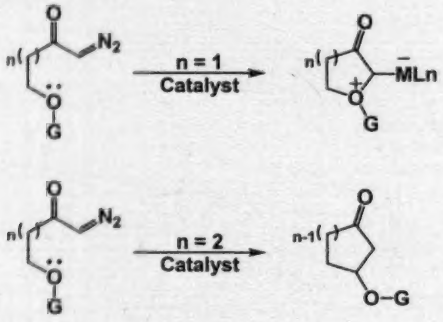


Figure 1.7: C-H insertion competes with formation of >5-membered ylides.

Other factors affecting the course of reactions involving oxonium ylides include the substitution at R_1. Typically this is either a proton (making the substrate an α-diazo ketone) or an ester (making the starting substrate an α-diazo-β-keto ester). In many cases, this substituent has a significant impact on the yield of the reaction. Another factor influencing the outcome the reaction is the substitution at R_2. When substituted, steric crowding can have a marked impact on the rearrangement process, often affording diastereo-enriched products (Figure 1.8).

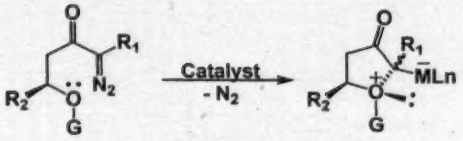
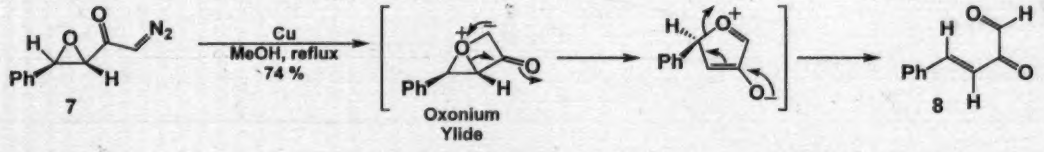


Figure 1.8: Structural factors that impact the outcome of oxonium ylide processes.

1.3. Synthesis Employing Monocyclic Oxonium Ylides

1.3.1. Preliminary Investigatons

The early studies by Nozaki and Kirmse (Scheme 1.1) provided evidence that rearrangements of catalytically-generated oxonium ylides were possible. The example by Nozaki was a rare example of a high-yielding intermolecular [1,2]-shift process, whereas Kirmse obtained a mixture of the C-H insertion and rearrangement products. One of the first examples of the use of catalytically decomposed diazoketones for the generation of an intramolecular oxonium ylide in synthesis was by Zwanenburg.[19] An epoxide with a pendant diazoketone was treated with copper in MeOH heated at reflux. This resulted in the intramolecular formation of a 4-membered oxonium ylide which then underwent a fragmentation to afford the ketoaldehyde (**8**) (Scheme 1.2).

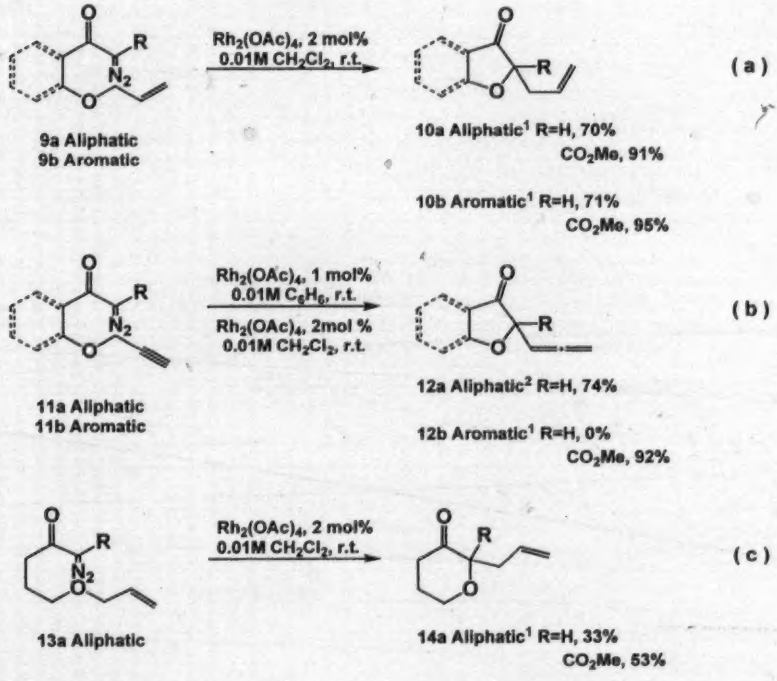


Scheme 1.2: The ylide formation / fragmentation sequence of Zwanenburg.

In 1986 Pirrung[20] and Johnson[21] demonstrated the potential of oxonium ylides in the synthesis of heterocycles. These two papers investigated many of the aspects of metallocarbene / onium ylide reactivity noted above. They showed that metallocarbenes react with an intramolecularly placed ethereal oxygen to form oxonium ylides, and that

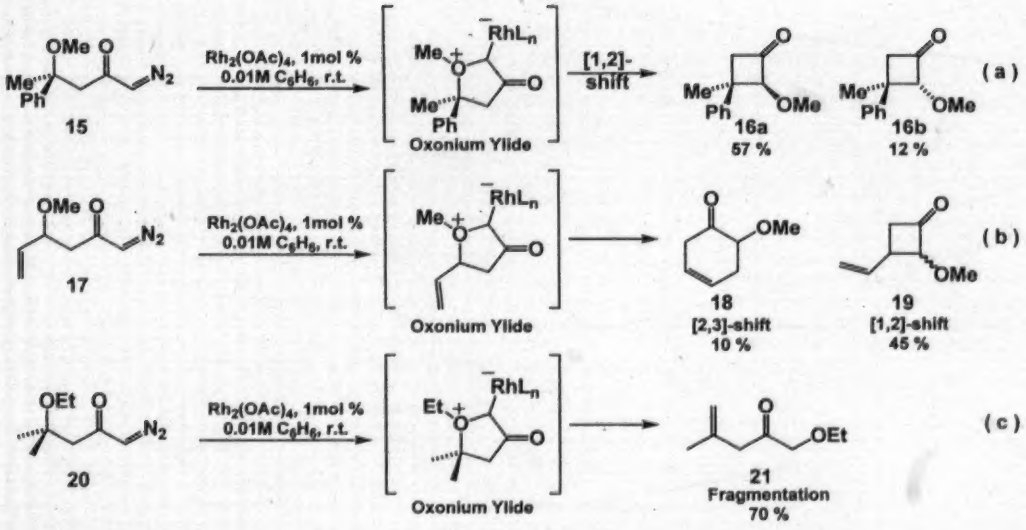
these ylides undergo both [1,2]-shifts and [2,3]-rearrangements. Since the publication of these two seminal papers, the transition metal-mediated carbene transfer to afford oxonium ylides has been the universally employed protocol. In our efforts toward advancing the field of the formation and rearrangement of oxonium ylides, we have devised an alternative to the use of diazoketones for the generation and rearrangement of ylides, which will be discussed in Chapter 3.

Pirrung and Johnson both demonstrated the exocyclic [2,3]-sigmatropic rearrangement of allyl and propargyl ethers of aliphatic and aromatic substrates to generate 3-furanone and 3-pyranone products (Scheme 1.3). They also demonstrated the endocyclic benzyl [1,2]-shift and allyl [2,3]-rearrangement. Johnson attempted an alkyl [1,2]-shift, which failed, and afforded the product of an α',β-fragmentation pathway (Scheme 1.4).



[1]: Johnson[21] [2]: Pirrung[20]

Scheme 1.3: Selected exocyclic [2,3]-shifts of Pirrung and Johnson.



Scheme 1.4: Endocyclic [1,2]-shift, [2,3]-shift and fragmentation reactions observed by Johnson.[21]

1.3.2. The [2,3]-Sigmatropic Rearrangement

As suggested earlier, one of the key factors controlling the outcome of ylide-formation / rearrangement processes is the migrating group. Groups that are capable of undergoing the low-energy, symmetry-allowed [2,3]-rearrangement typically do so with ease. The most commonly seen migrating group for this rearrangement is the allyl group (Figure 1.9). For a given allylic [2,3]-rearrangement, it could also be proposed that the rearrangement is occurring by way of a [1,2]-shift upon formation of the oxonium ylide. The consistent observation of allylic inversion during the rearrangement suggests that it does occur by a pericyclic process, as [2,3]-rearrangements are known to do (Figure 1.9). It can be argued that allyl inversion could also result from recombination during a [1,2]-shift at the more substituted terminus of the allyl group. This latter proposal is dispelled by the fact that when propargyl substrates undergo [2,3]-rearrangements, only allenic products are obtained (Scheme 1.3, eq. b).

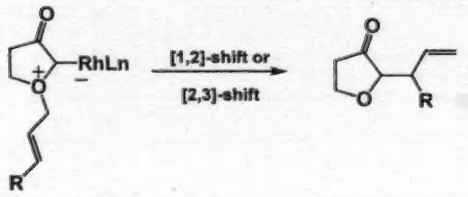


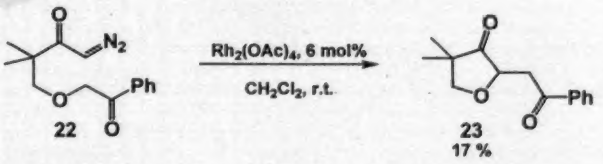
Figure 1.9: The modes of rearrangement for the allylic shift.

Poor substrate design can also have significant impact on the outcome of the facile [2,3]-shift. For substrate **17** (Scheme 1.4, eq. b), the [2,3]-rearrangement was not the dominant reactive pathway, the substrate undergoing a vinyl [1,2]-shift instead, affording **19**. The decreased occurrence of the [2,3]-rearrangement product **18** likely resulted from the oxonium ylide being a rigid, cyclic structure, and the reacting terminus of the allyl group was unable to enter into bonding proximity with the ylidic carbon. Other instances of this reactivity will be examined in detail in a later section.

1.3.3. The Stevens [1,2]-Shift

Johnson[21] investigated two substrates for the [1,2]-shift. Given the proposed[22] biradical mechanism of a Stevens [1,2]-shift, only migrating groups effective at stabilizing the radical intermediate would be expected to undergo migration. As illustrated in Scheme 1.4 (eq. a), Johnson showed that the benzyl shift proceeded to give **16a,b** in good yield. The alkyl [1,2]-shift failed to occur, affording only **21**, the product of a fragmentation pathway (Scheme 1.4, eq. c). These results illustrate that the choice of migrating group can have a significant impact on the outcome of a [1,2]-shift of a substituted oxonium ylide. Dhavale and co-workers[23] subsequently showed that electron rich (alkoxy-substituted) and electron poor (nitro- or carbomethoxy-substituted) benzyl substrates are both effective stabilizing groups in the [1,2]-shift. While 3° alkyl carbons are relatively stable radicals, it appears that this stabilization is not sufficient to lower the activation barrier for bond homolysis in the Stevens rearrangement. As shown above, vinyl [1,2]-shifts can also occur, presumably when the oxonium ylide formed is unable to accommodate the geometric requirements of the [2,3]-rearrangement. West[24] further

showed that migrating carbons substituted with electron withdrawing groups (**22**) are less effective at facilitating the Stevens rearrangement (Scheme 1.5).

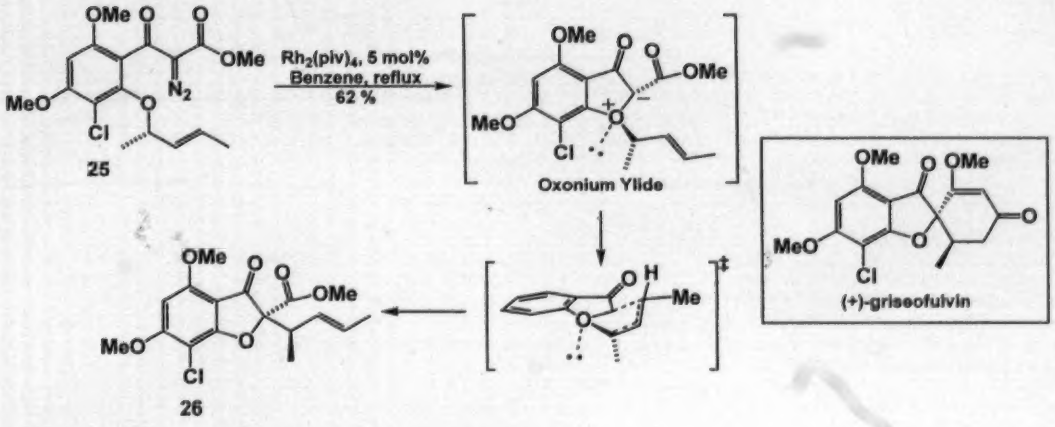


Scheme 1.5: The [1,2]-shift of an electron deficient migrating group.

In summary, both allyl and propargyl substrates readily undergo the symmetry-allowed, low-energy [2,3]-sigmatropic rearrangement to afford products of allyl-inversion. For the [1,2]-shift, the best migrating groups are those capable of stabilizing the radical intermediates through resonance. This typically includes benzyl groups and allyl groups (in rare cases where the [2,3]-shift is geometrically disfavored). Heteroatom (N, O, S) oxonium ylides are also highly effective in promoting the [1,2]-shift, and these cases will be discussed later.

1.3.4. The Synthesis of (+)-Griseofulvin

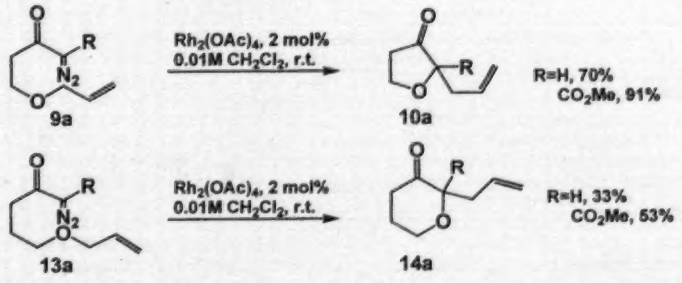
Pirrung and co-workers undertook the first use of the tandem oxonium ylide formation and [2,3]-shift protocol in a total synthesis of the natural product (+)-griseofulvin.[25] Upon intramolecular 5-membered oxonium ylide formation, the ylide underwent a diastereoselective [2,3]-sigmatropic rearrangement. Upon treatment of **25** with rhodium pivalate, the desired product **26** was recovered as a single regio- and stereoisomer in 62 % yield (Scheme 1.6). This stereochemistry is rationalized via an oxoniabicyclo[3.3.0]octane transition structure, in which the methyl group is found on the sterically least congested convex face of the ylide.



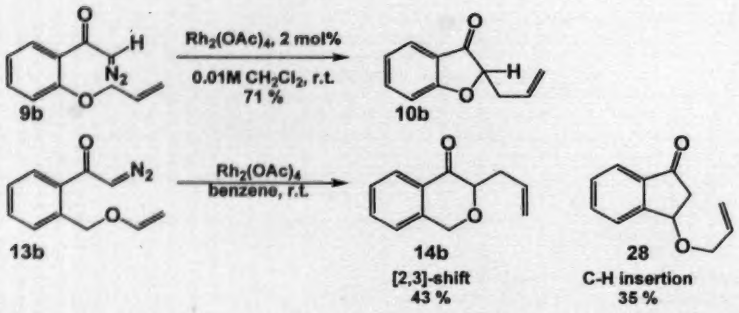
Scheme 1.6: The synthesis of (+)-griseofulvin.

1.3.5. The Value of *n*: Oxonium Ylide Ring Size

The effect of oxonium ylide ring size on the formation and rearrangement of oxonium ylides has been investigated. There was precedent that suggested there would be a kinetic preference for 5-membered oxonium ylide formation, or for competing reactive pathways when ylide formation was not possible. Pirrung[20] demonstrated this when he showed that 5-membered C-H insertion competes with 6-membered oxonium ylide formation (Scheme 1.7). A subsequent study by Padwa[26] can be compared with Pirrung's result (Scheme 1.3, eq. c) for the analogous aromatic-fused system. Where 5-membered ylide formation and rearrangement was facile, the homologous 6-membered ylide formation suffered from competing 5-membered C-H insertion (Scheme 1.8).

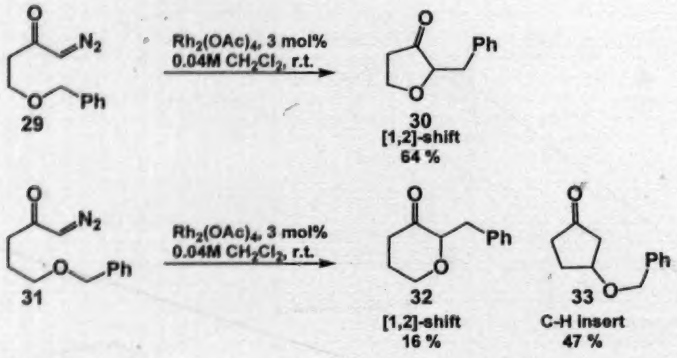


Scheme 1.7: 5-Membered vs 6-membered oxonium ylide formation in the aliphatic allyl [2,3]-shift.



Scheme 1.8: 5-Membered vs 6-membered oxonium ylide formation in the aromatic allyl [2,3]-shift.

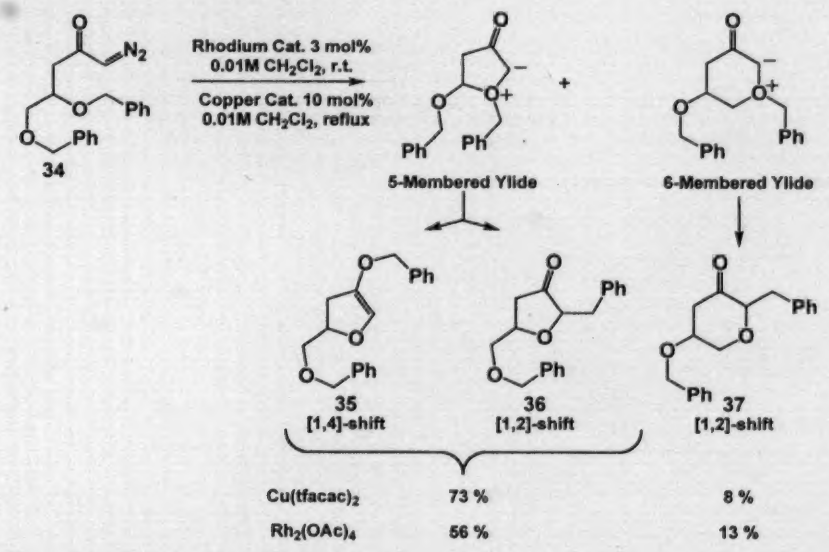
West[24] has also illustrated this point. For the benzyl ether substrate **29**, 5-membered ylide formation and subsequent rearrangement occurred to give **30** in 64 % yield (Scheme 1.9). Again, ylide formation of the homologous substrate **31** suffered from competing C-H insertion, giving the pyran-3-one product **32** in 16 % yield, and the C-H insertion product **33** in 47 % yield.



Scheme 1.9: 5-Membered vs 6-membered oxonium ylide formation in the aliphatic benzyl [1,2]-shift.

There is another recent example by West[27] in which 5- and 6-membered ylide formation was possible. A strong preference for 5-membered ylide formation and subsequent rearrangement (to give **35** / **36**) for the bis(benzyl ether) substrate **34** was

observed (Scheme 1.10). (The alternative recombination possibility for the bi-radical intermediate of the [1,2]-shift, the [1,4]-shift product **35**, has been included in the ratio of 5- to 6-membered ylide derived products. The occurrence of this product will be discussed later.)



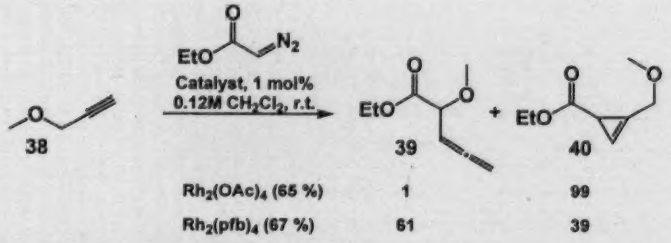
Scheme 1.10: Competitive 5-membered vs 6-membered oxonium ylide formation in the aliphatic benzyl [1,2]-shift.

These examples illustrate that placement of the reacting oxygen atom five atoms from the metallocarbene center is preferred to achieve effective ylide formation. This is not always possible in synthesis, which led several groups to investigate the dramatic effects that catalysts can have on the outcome of oxonium ylide processes.

1.3.6. The Effect of Catalyst

The development of new catalysts greatly advanced this methodology as it enabled optimization for chemoselective processes, as well as induction of asymmetry during the [1,2]- or [2,3]-shift. The generation of tetrahydrofuran-3-ones was shown to be an efficient catalytic process using various rhodium acetate catalysts. However, it was shown that the preparation of tetrahydropyran-3-ones suffered from the competing C-H insertion processes for both the [1,2]- and [2,3]-shifts. It was envisioned that one might

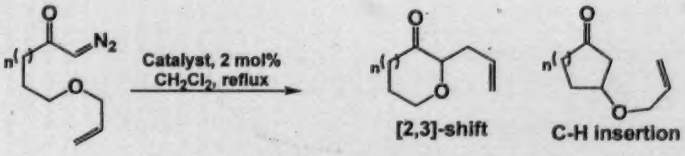
be able to promote ylide formation while reducing the likelihood of competing reactions by changing the nature of the catalyst. According to Doyle,[28] in changing the electronic nature of the catalyst the metallocarbene becomes a harder acid that is more likely to form an oxonium ylide with the ethereal oxygen. This is believed to have been the case based on the product distributions for the study of the intermolecular ylide formation and rearrangement of ethyl diazoacetate and methyl propargyl ether. Treating a mixture of these reagents with $Rh_2(OAc)_4$ afforded a 99:1 mixture of **39** and **40**, respectively, in 65 % yield. On the other hand, the $Rh_2(pfb)_4$ (rhodium perfluorobutyrate) catalyst gave a 39:61 mixture, favoring **39**, in 67 % yield (Scheme 1.11).



Scheme 1.11: Comparison of fluorinated vs non-fluorinated ligands in the rhodium-catalyzed intermolecular [2,3]-shift.

Further advancements of catalyst development came when Clark[29,30] and West[31] disclosed the use of various copper catalysts for this tandem process. It had been previously shown that copper acetylacetonato complexes were capable of promoting oxonium ylide formation. [11,12,32] As such, these catalysts were tested in the carbene transfer of diazocarbonyls for the generation and rearrangement of oxonium ylides. Pirrung[20] and Johnson[21] showed that competing C-H insertion was a major reactive pathway in 6-membered oxonium ylide formation under $Rh_2(OAc)_4$ catalysis (**13a** to **14a**). Conversely, Clark demonstrated that upon treatment of **13a** with $Cu(acac)_2$, the ylide derived product **14a** was generated in 61 % yield with only 12 % of the C-H insertion product **41**. In analogy with Doyle's result, increasing the fluorine content on the catalyst favored ylide formation (Scheme 1.12). Treatment of **13a** with $Cu(tfacac)_2$ afforded 78 % of **14a**, and treatment with $Cu(hfacac)_2$ afforded **14a** in 83 % yield. Clark then went on to show that while 7-membered ylide formation with $Rh_2(OAc)_4$ was

ineffective, the copper acetylacetonato (acac) catalysts were moderately to highly effective. $Cu(acac)_2$ catalysis gave **43** in 18 % yield whereas the fluorinated $Cu(hfacac)_2$ catalyst gave **43** in 76 % yield with only 3 % of the C-H insertion product **44**. The most dramatic example of this catalyst effect was seen for the substrate **45**. Where $Rh_2(OAc)_4$, $Cu(acac)_2$, $Cu(tfacac)_2$ failed to give the product of rearrangement, $Cu(tfacac)_2$ afforded product **46**, formed via an intermediate 8-membered oxonium ylide, in 40 % yield (Scheme 1.12).



	n	Catalyst	yield (%)		yield (%)	
13a	1	$Cu(acac)_2$	14a	61	41	12
"	1	$Cu(tfacac)_2$	"	78	"	0
"	1	$Cu(hfacac)_2$	"	83	"	0
42	2	$Cu(acac)_2$	43	18	44	61
42	2	$Cu(tfacac)_2$	"	38	"	41
42	2	$Cu(hfacac)_2$	"	76	"	3
45	3	$Cu(hfacac)_2$	46	40	47	0

Scheme 1.12: Copper catalysts effective in promoting the [2,3]-shift in systems of increasing ring size.

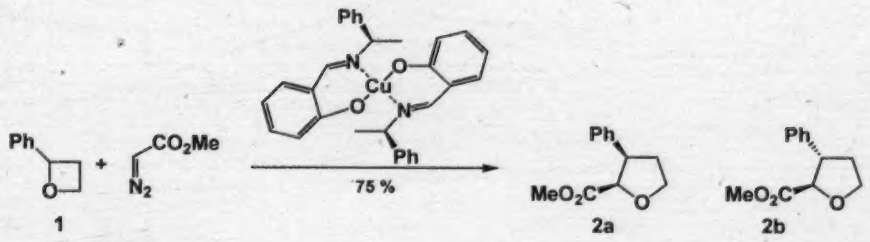
These examples demonstrate how altering the electronics of a catalyst can alter the outcome of a reaction. The results of Clark's study illustrate that the copper acetylacetonato (acac) catalysts are more likely to afford the product of ylide formation than are the previously employed rhodium catalysts. The increasing fluorine content appears to promote ylide formation proportionate with increasing fluorine density, while providing an inversely proportionate amount of the C-H insertion product. The most notable example of this catalyst effect is the ability to generate 8-membered rings by this method.

The degree to which metallocarbenes of these copper catalysts undergo ylide formation may be explained as an extension of the electrophilic / hard acid argument

suggested by Doyle. One necessary assumption is that the electrophilicity of the metallocarbene is directly related to the observation of ylide-derived products. Based on product distributions for substrate **13a**, it can be suggested that the metallocarbenes derived from copper catalysts are inherently more electrophilic than are the ones from rhodium catalysts. One possible explanation for the increased electrophilicity could be that Rh(II) makes 18 electron carbenoids, whereas Cu(I) makes 16 electron carbenoids. The electrophilicity rationale also holds true throughout the series of increasing fluorine content on the copper catalysts. As the fluorine density around the copper increases, one might propose there is less donation of electron density from the ligands to the copper atom, making the copper center more electrophilic. Therefore, one would also expect to see an increase in the yield of ylide-derived products as the fluorine content increases, which was in fact observed. This explanation serves only as a simple model for the metallocarbene process at hand and there are many cases where product distributions contrast with this hypothesis.

1.3.7. The Induction of Asymmetry in Rearrangements of Oxonium Ylides

These previous examples show how variation of the catalyst can lead to significant improvements in the occurrence of ylide derived products. Rhodium and copper catalysts have also been shown to induce asymmetry in the products of carbenoid processes with the use of chiral ligands. In 1968, Nozaki, Noyori and co-workers employed catalysts with chiral ligands for the transformation of **1** to **2a,b** (Scheme 1.13).[32] Though the enantiomeric excesses were not reported, this was a landmark investigation as it was the first (outside the area of polymer chemistry) to show organometallic catalysis could be made asymmetric by employing chiral ligands. The subsequent developments of chiral ligands for asymmetric induction in onium ylide processes are many.[33] Catalysts have been developed which can afford products in up to 80 % ee for the [1,2]-shift, as well as up to 98 % ee for the [2,3]-shift. Based on the ability of chiral catalysts to effect asymmetry in the products of carbenoid processes, it was suggested that the metal was bound (or associated) with the substrate when the product-forming rearrangement occurred.



Scheme 1.13: The first use of chiral ligands in transition metal-catalyzed oxonium ylide processes.

1.4. The Mechanism of Ylide Formation and Rearrangement

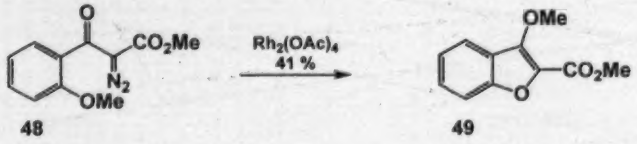
1.4.1. Primary Considerations

When contemplating the mechanism of the oxonium ylide / rearrangement process, the following experimental observations must be considered: the energy barrier for inversion of an oxonium centre is presumed to be low;[34] the [2,3]-shift is a low-energy, symmetry allowed sigmatropic rearrangement; the [1,2]-shift is symmetry forbidden, and is believed to proceed via a bond homolysis then recombination pathway; the chemo- and stereo-selectivity changes as a function of catalyst employed; and asymmetric induction is possible when using a chiral transition metal catalyst. Any mechanistic proposal must account for these observations.

1.4.2. Ylide Reversibility

The rearrangement process is initiated by the formation of a metallocarbene by carbene transfer. Subsequent intramolecular attack by an ethereal oxygen affords an oxonium ylide. The reversibility of oxonium ylide formation has been proposed by several groups to account for the isolation of anomalous products. For example, in the first asymmetric synthesis of (+)-griseofulvin[25] (Scheme 1.6), Pirrung suggested that

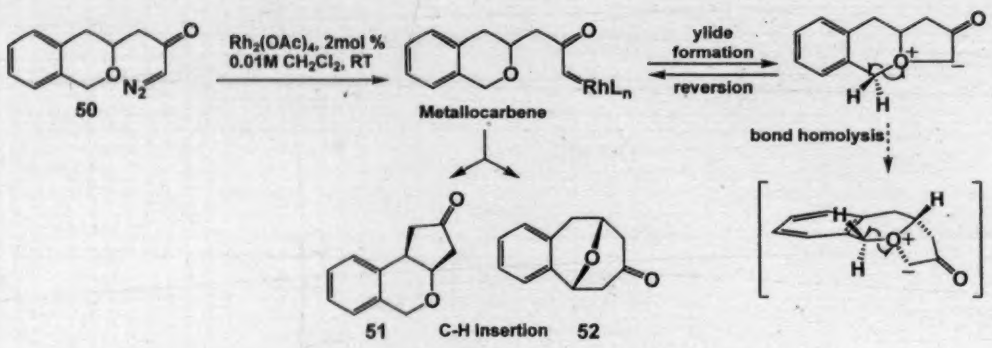
ylide formation was reversible due to the lack of an expected side product. A model study indicated that an *o*-methoxy group could undergo ylide formation with a subsequent [1,4]-shift (Scheme 1.14), but none of **49** was observed during the synthesis. Pirrung proposes that ylide formation is reversible, and that a Curtin-Hammett situation results. The activation barrier for the [2,3]-rearrangement is lower than that for the bond homolysis believed necessary for the [1,4]-shift to occur. These energetic arguments account for the isolation of only one product.



48 49

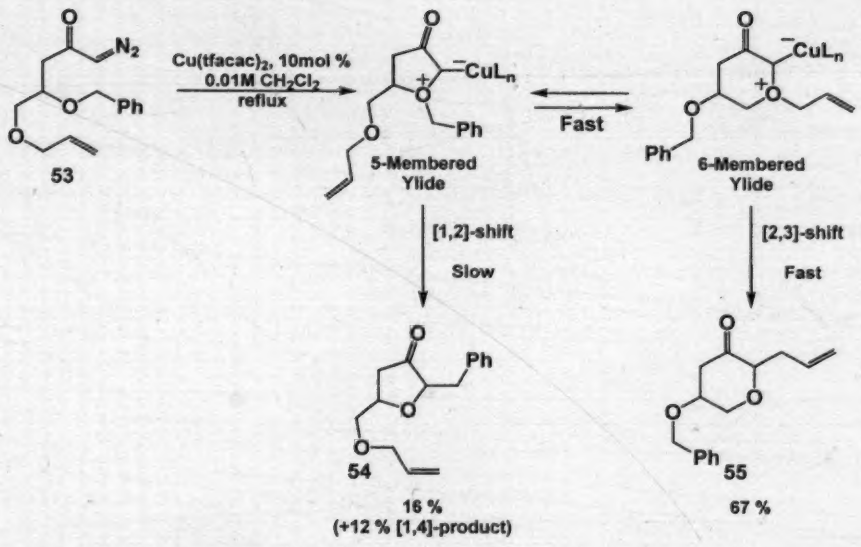
Scheme 1.14: Model study to determine the outcome of methyl-substituted oxonium ylide formation. The product observed is from a [1,4]-shift.

West[35] has suggested ylide reversibility to account for the observation of C-H insertion products in attempting the [1,2]-shift on **50**. He proposed the 5-membered oxonium ylide formation occurred as usual, but the benzyl radical forming upon bond homolysis does not experience any stabilization as this scissile bond is orthogonal to the pi-system of the phenyl ring. In this case the ylide can revert to the metallocarbene, which then decomposes through the available C-H insertion pathways to give **51** and **52** (Scheme 1.15).



Scheme 1.15: C-H insertion products isolated from carbene transfer on **50**. Ylide reversibility is proposed to account for the observation of **51** and **52**.

A competition study undertaken by West[27] furthered the notion of oxonium ylide reversibility. The rearrangement of **53** under copper catalysis afforded the 6-membered [2,3]-rearrangement product **55** as opposed to the [1,2]-shift product **54**, resulting from formation of a 5-membered oxonium ylide. If this were under Curtin-Hammett control, and the rate of equilibration between copper-based oxonium ylides was fast, it could explain why the [2,3]-rearrangement dominated, having the lower activation barrier, despite the known propensity for the formation of 5-membered ylides (Scheme 1.16).



Scheme 1.16: Competition study between 5-membered benzyl [1,2]- and 6-membered allyl [2,3]-shifts. Ylide reversibility is proposed to account for the formation of 55.

1.4.3. The Mechanism of the [2,3]-Sigmatropic Rearrangement

The rearrangements possible upon ylide formation will now be considered, starting with the [2,3]-sigmatropic rearrangement. This is a low-energy, symmetry-allowed process that occurs by a sigmatropic rearrangement. Because the criteria for this mechanism require the presence of the metal at the time of bond formation, the following proposals are among the mechanisms that could be operative. Should transition metal dissociation from the oxonium ylide occur, this would leave a free ylide. If the [2,3]-rearrangement process is faster than the rate of oxonium inversion, a chiral environment might be conserved and the metal-assisted criteria will be met (Figure 1.10, Path a). Another suggestion[21] is a metal-bound, concerted migration process for the [2,3]-sigmatropic rearrangement with concomitant metal-carbon bond cleavage. This again accounts for the metal-associated requirement of the mechanism (Figure 1.10, Path b).

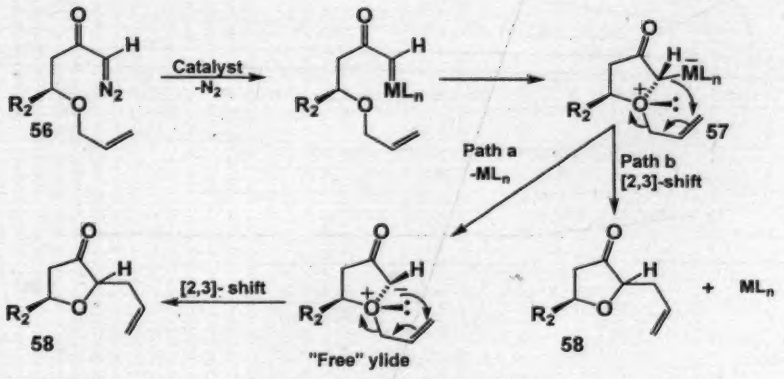
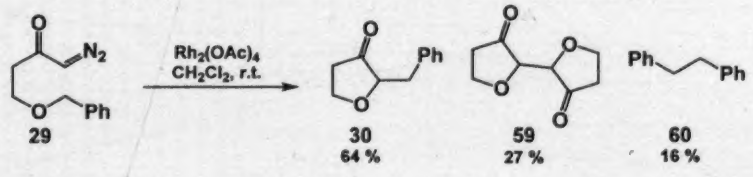


Figure 1.10: The proposed mechanisms for the [2,3]-sigmatropic rearrangement.

1.4.4. The Mechanism of the Stevens [1,2]-Shift

The transition metal-catalyzed Stevens [1,2]-shift mechanism is believed to proceed via bond homolysis at the oxonium center, affording a radical pair. This is supported by the observations of West and others who have recovered homodimeric products suggestive of radical precursors (Scheme 1.17).[24]



Scheme 1.17: Homodimeric products recovered by West and co-workers during a benzyl [1,2]-shift.

The mechanism of the [1,2]-shift begins with the formation of an oxonium ylide. As with the [2,3]-rearrangement, one can propose that the next step is metal dissociation, leaving behind a free ylide in an initially chiral environment. Bond homolysis then results in a radical pair trapped within a solvent cage. If recombination happens with chiral memory the product of the [1,2]- or [1,4]-shifts can be observed. If these radicals diffuse

from the solvent cage, the homo-dimer recombination pathway is enabled (Figure 1.11). To account for asymmetric induction, it is necessary for bond homolysis and recombination to occur on a faster timescale than oxonium inversion. Therefore, it is likely that the metal is still present at the time of bond formation.

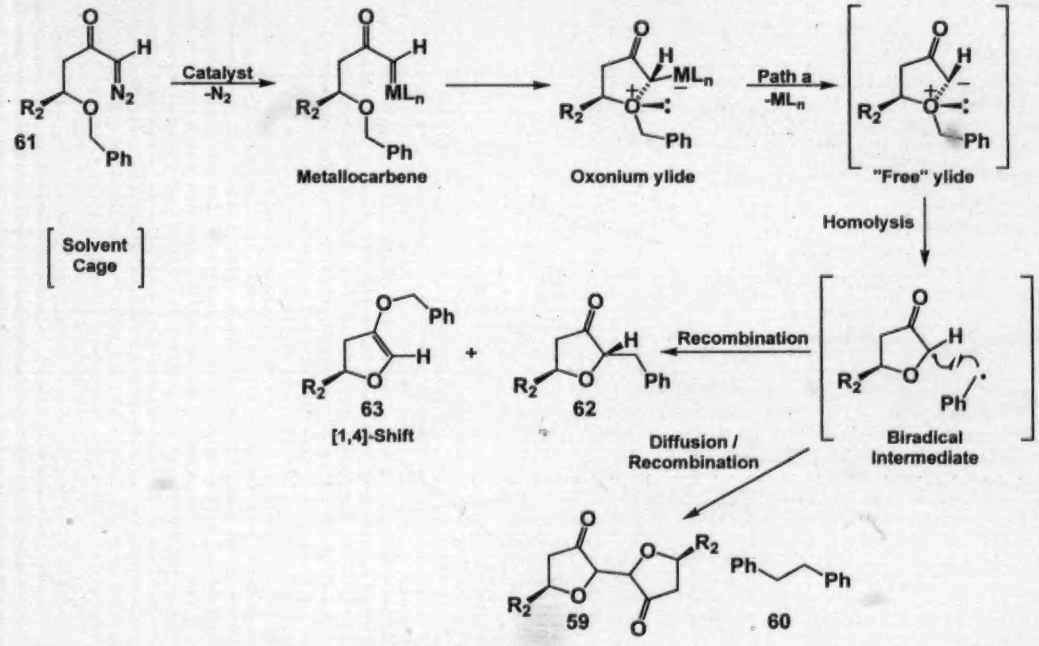


Figure 1.11: The transition metal-free [1,2]-shift mechanism.

If the metal remains associated through to the point of the [1,2]-shift, there are at least two pathways to be considered. If the metal-bound oxonium ylide undergoes benzyl-transfer, the product **62** would be obtained upon reductive elimination. If enolization occurs, this can eliminate to give the [1,4]-shift product **63** (Figure 1.12). This direct metal-assisted mechanism may be operative, but it fails to account for the potential occurrence of homo-dimers.

It may then be the case that **61** undergoes homolysis to afford a radical pair in which one of the entities is stabilized by the transition metal. Radical recombination in the presence of the metal accounts for asymmetric induction, and if the radical pair

diffuses from the solvent cage prior to recombination, the homodimeric products **59**, **60**, or the [1,4]-shift product **63** can also be formed (Figure 1.13).

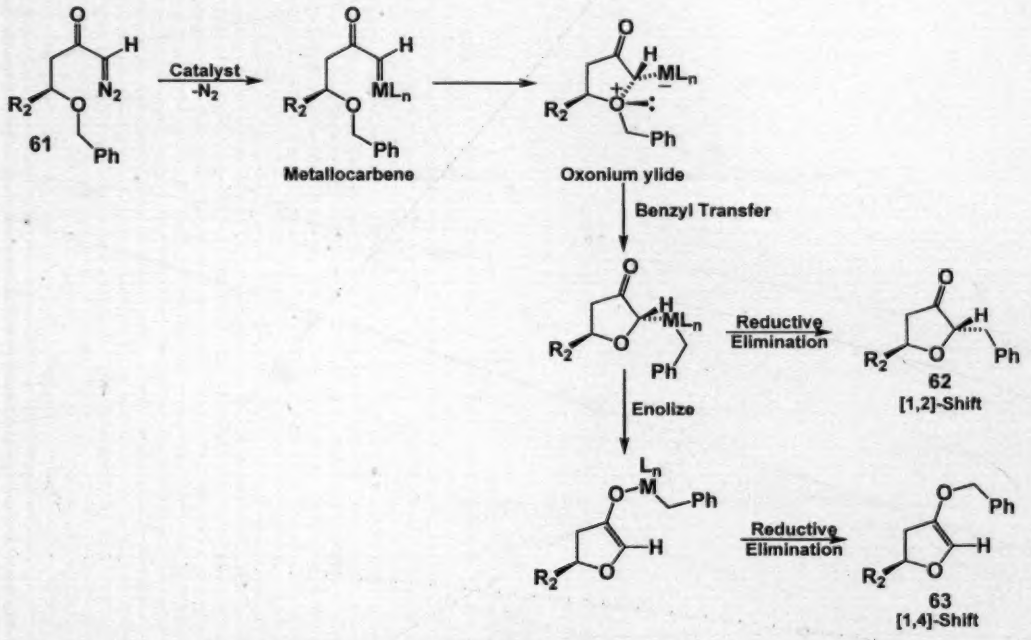


Figure 1.12: The benzyl transfer / reductive elimination proposal for [1,2]-shift

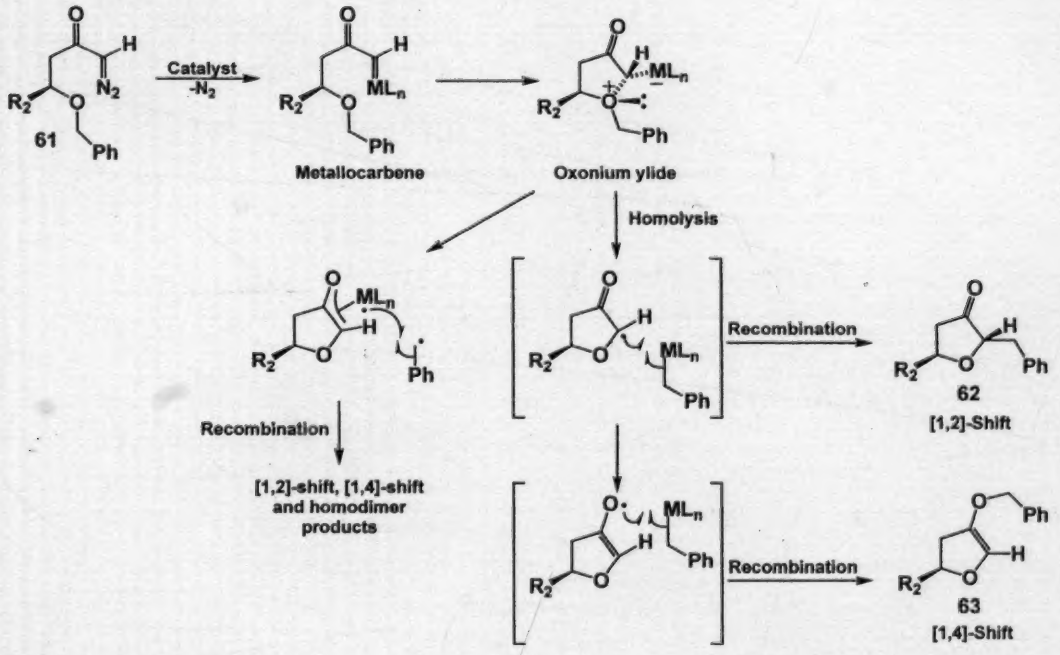
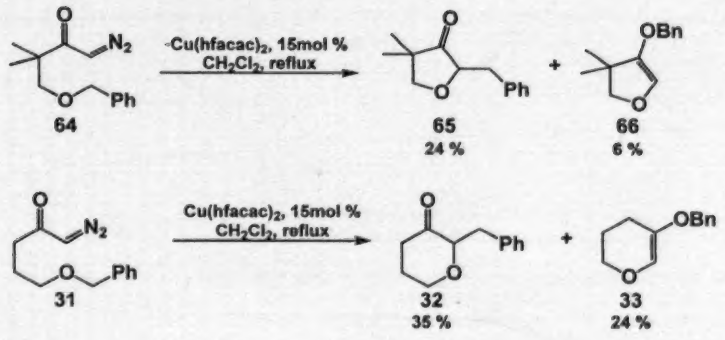


Figure 1.13: The metal-assisted homolysis / recombination proposal for the [1,2]-shift.

The mechanism of the [1,2]-shift of oxonium ylides is a complicated process for which there is very little direct information. Mechanistic proposals are typically based on product distribution, not spectroscopic evidence. These proposals highlight some of what has been suggested in the literature; the actual situation in the flask may be substantially more complicated.

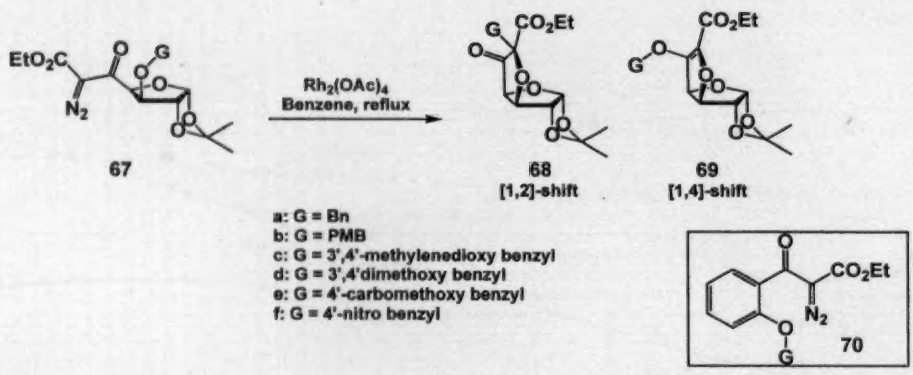
1.4.5. [1,2]- vs [1,4]- Shifts

Pirrung conducted a model study during the synthesis of (+)-griseofulvin (Scheme 1.14), probing the behavior of a substrate expected to form an O-methyl ylide. He showed that when substrate **48** was treated with $Rh_2(OAc)_4$, product **49**, arising from a [1,4]-shift, was observed. Such [1,4]-shift products were also observed by West[31] when **64** and **31** were treated with $Cu(hfacac)_2$ (Scheme 1.18).



Scheme 1.18: [1,4]-Shift products isolated from [1,2]-shift processes.

Dhavale and co-workers[23] sought to investigate this competitive [1,2]- vs [1,4]-shift by varying the migratory aptitude of the ether substituent, and observing the effect this has on the product distribution. They showed that for substrates **67**a-f, the yields of the reactions were consistent (75-82 %), but the ratio of [1,4]-shift products was variable. In substrates where greater electron density was imparted on the migrating carbon through resonance, the [1,4]-shift product dominated (Scheme 1.19, entries b-d). The opposite was true for substrates where decreased electron density was imparted on the migrating carbon (Scheme 1.19, entries e,f). Dhavale showed this trend also to be true for a similar competition study on substrates **70**, by again varying the substitution on the migrating group (G). In this instance the [1,4]-shift product was observed in all cases, even when G = Me.



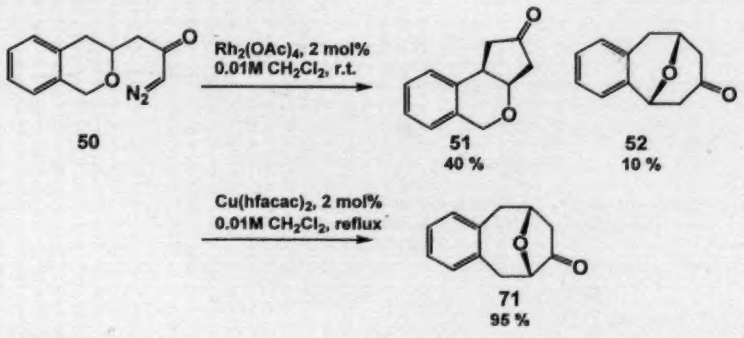
Scheme 1.19: Promoting for [1,4]-shift products through variably-substituted benzyl [1,2]-shifts.

Because [1,2]-shifts are believed to proceed via a homolysis / recombination mechanism, the electronic effects observed by Dhavale might be interpreted as stabilization of a benzyl radical through resonance, and the formation of the [1,4]-products resulting from a longer-lived radical pair. In the Pirrung and Dhavale cases where a methyl ether underwent a [1,4]-shift, it is likely the rearrangement occurred with greater stabilization of the biradical intermediates by the transition metal catalyst.

1.4.6. Evidence that the Copper and Rhodium Mechanisms are Different

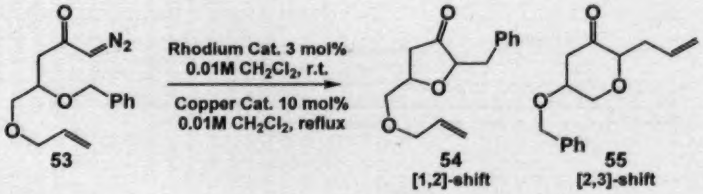
Many of the results thus far show differences in the product distribution under rhodium and copper catalysis. One example is Clark's studies on the effects of copper catalysts in the formation of 6-8 membered oxonium ylides, in cases where rhodium catalysis fails.[36] There are numerous examples of product distributions being variable with changing catalyst, especially when other carbenoid processes are competing with ylide formation. In one notable example, West[31,35] showed that even when 5-membered oxonium ylide formation is involved, the products of rhodium and copper catalyzed reactions can differ completely for the same substrate (Scheme 1.20). He showed that treatment of benzodihydropyran **50** with $Rh_2(OAc)_4$ afforded the products of C-H insertion pathways **51** and **52**. A subsequent experiment in which this same substrate was

treated with the $Cu(hfacac)_2$ showed that only the product derived from the [1,2]-shift pathway (**71**) was obtained.



Scheme 1.20: Differing product distributions for Rh and Cu catalysts.

In West's competition study, it was observed for the rhodium catalyzed carbene transfer on **53** that a diastereomeric mixture of **54** was isolated as the major product (Scheme 1.21).[27] Treatment of **53** with $Cu(hfacac)_2$ also afforded **54** as the major product. Interestingly, the $Cu(tfacac)_2$ catalyst gave the product of 6-membered ylide formation with subsequent [2,3]-rearrangement as the major product (**55**). The selectivity of $Cu(tfacac)_2$ for 6-membered ylide formation when a subsequent [2,3]-shift is possible has also been observed by Clark[37] and West.[38]



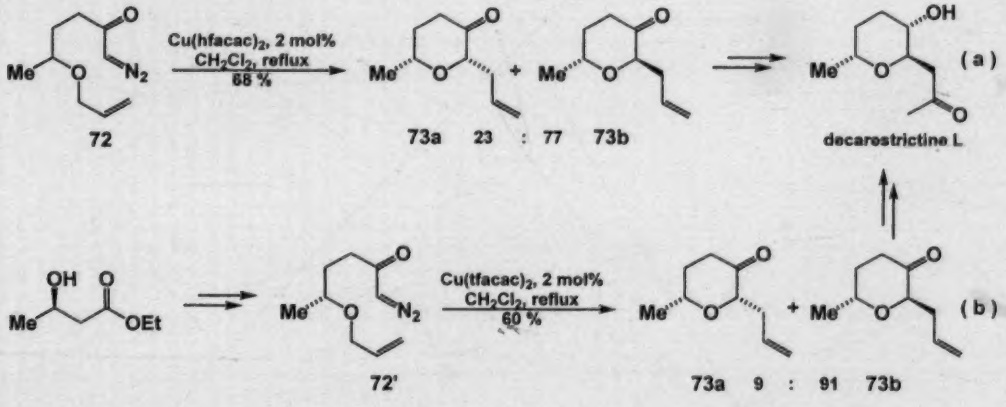
$Rh_2(OAc)_4$	50	27
$Cu(tfacac)_2$	28[a]	67
$Cu(hfacac)_2$	57[a]	29

[a]: includes [1,4]-shift product

Scheme 1.21: [1,2]-Shift vs [2,3]-shift competition study using Rh and Cu catalysts.

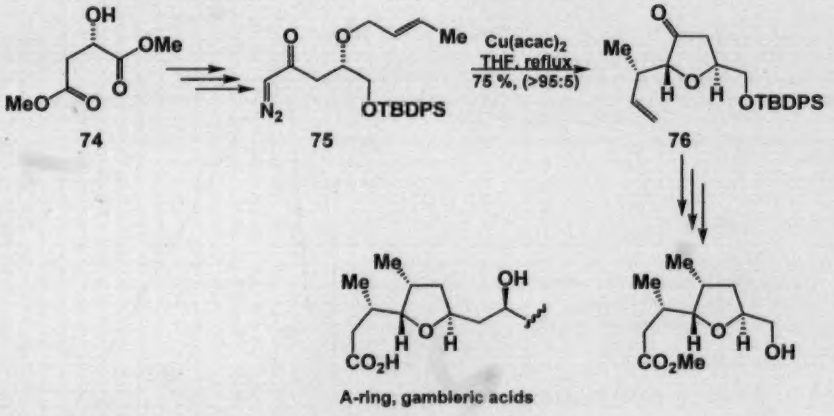
1.4.7. Selected Applications in Synthesis

These examples suggest that the mechanisms of the rhodium and copper catalyzed rearrangements may be different and that anomalous reactivities are often encountered. When attempting a novel metallocarbene-mediated transformation, it appears advisable to try several catalyst systems. While the products of carbenoid reactions are not always predictable, the differences in product distribution can be exploited synthetically to obtain different products from the same substrate. Using the knowledge gained in the studies of monocyclic oxonium ylides, there have been several uses of oxonium ylides in either total syntheses, or for the synthesis of specific structural motifs. One of these was the total synthesis of (+)-griseofulvin[25] (Scheme 1.6). Another was Clark's enantioselective synthesis of (+)-decarestrictine L.[37, 39] The original diastereoselective synthesis showed that when **72** was treated with $Cu(hfacac)_2$, rearrangement occurred to generate pyran-3-one **73a,b** in 68 % yield, as a 77:23 mixture of stereoisomers, favoring the *trans* **73b** (Scheme 1.22, eq. a). Clark later presented the enantioselective synthesis in which diazoketone **72'** was prepared from commercially available ethyl (*R*)-3-hydroxybutyrate over a series of steps. Treatment of this with $Cu(tfacac)_2$ afforded the desired *trans* isomer **73b** in 60 % yield (as a 91:9 ratio), which was then carried on to decarestrictine L (Scheme 1.22, eq. b).



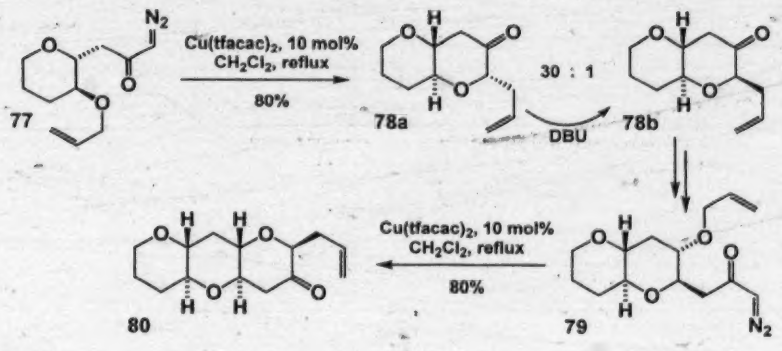
Scheme 1.22: The racemic and enantioselective syntheses of (±)-decarestrictine L

Clark has carried out a diastereoselective synthesis of the A-ring fragment of the decacyclic gambieric acid polyether natural products (Scheme 1.23). This was accomplished using a tandem 5-membered oxonium ylide formation / [2,3]-rearrangement approach. Starting from commercially available **74**, this underwent a diastereoselective rearrangement upon oxonium ylide formation from **75** to give **76** as the major product in a 95:5 ratio.[40]



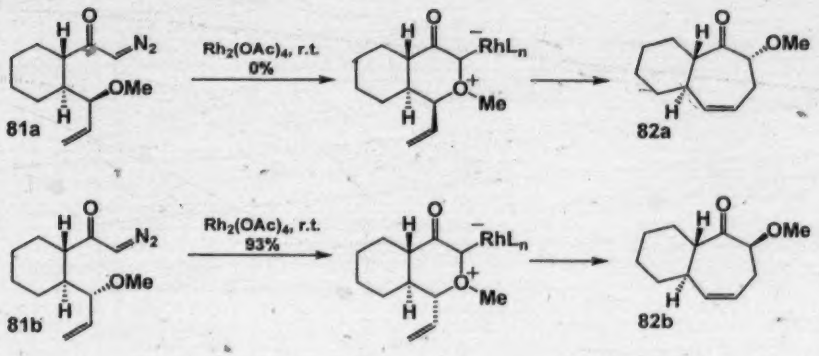
Scheme 1.23: Synthesis of the A-ring of the gambieric acids.

West and co-workers have demonstrated that the ylide formation / [2,3]-sigmatropic rearrangement protocol is effective for the synthesis of polypyran motifs commonly found in polyether marine ladder toxins (Scheme 1.24).[38] Treating **77** with $Cu(tfacac)_2$ afforded **78a,b** in a 30:1 ratio via a diastereoselective [2,3]-rearrangement. The excellent selectivity was fortuitous, though the product required isomerization with DBU because the stereochemistry observed in **78b** is common to the polyether natural products. In their attempts to develop an iterative polypyran synthesis, they converted the *trans* isomer into diazoketone **79**, which also underwent rearrangement to give the tris-pyran **80** as a single diastereomer in 80% yield.



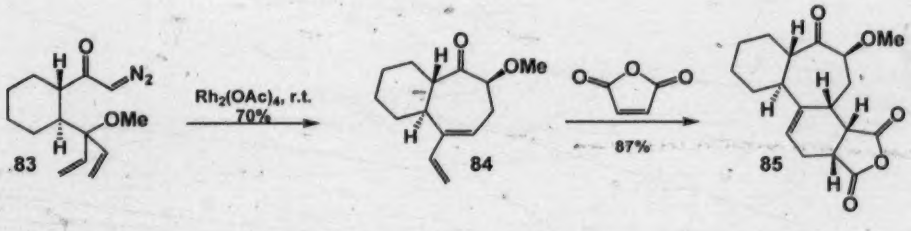
Scheme 1.24: Iterative approach to the polypyran motif.

Clark has used the original example of Johnson (Scheme 1.4, eq. b) as a template for ring expansion using an endocyclic [2,3]-shift, so as to enable entry into specific structural motifs. He attempted to generate the homologous 7- and 8-membered monocyclic carbocycles, and found that this strategy was only moderately effective. Clark proposed this to be the result of the oxonium ylide and vinyl groups being unable to suitably orient themselves within bonding distance, so that the endocyclic [1,2]-shift can compete. To test this hypothesis, Clark[41] examined the diastereomeric substrates **81a** and **81b** whose reacting conformations would be known due to the preferred cyclohexyl conformation. The results suggest that the relative configurations of the stereogenic centers afford a low energy reactive pathway for one of the diastereomers (giving product **82b** in high yield) and none of the other [2,3]-shift product **82a** (Scheme 1.25). This stereochemical analysis also suggests an optimal geometry for bond rearrangement, possibly accounting for the high yield of **82b**, even though it requires 6-membered oxonium ylide formation.

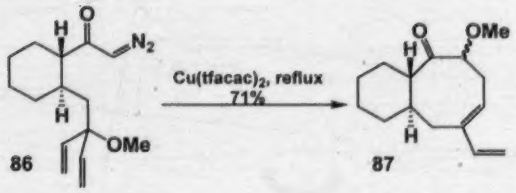


Scheme 1.25: Conformational analysis of endocyclic [2,3]-shifts

This conformational impediment is eliminated when the substrate is doubly substituted with vinyl, so that in any conformation there should be a low-energy [2,3]-shift pathway available. The cyclohexyl-fused methodology was further expanded upon by Clark[41] where he showed that polycyclic scaffolds can be obtained from this process. The cyclohexyl-fused substrate **83** underwent the [2,3]-rearrangement, giving product **84** in 70 %. Furthermore, he showed that when this rearrangement is performed in the presence of maleic anhydride, a cascade ylide formation / rearrangement / Diels-Alder cycloaddition occurs to give the tetracycle **85** in 60 % yield (Scheme 1.26). The homologous sequence to afford **87** from **86** was also shown to be effective (Scheme 1.27). 7-Membered ylide formation was conducted under $Cu(tfacac)_2$ catalysis, giving product **87** in 71 % yield (with 20 % of the endocyclic [1,2]-shift product).

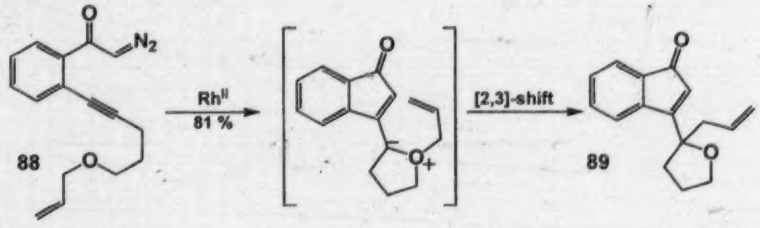


Scheme 1.26: A tandem endocyclic [2,3]-shift / Diels-Alder cycloaddition.



Scheme 1.27: An endocyclic [2,3]-shift to afford a bicyclo[6.4.0]dodecane skeleton.

Padwa[42] has also shown one other example of a cascade sequence involving oxonium ylides that terminates with a [2,3]-shift (Scheme 1.28). Upon carbene transfer, **88** undergoes ene-yne metathesis to give an alkyl metallocarbene that is trapped by a pendant ether affording an oxonium ylide which underwent a [2,3]-shift to give product **89**.



Scheme 1.28: Tandem intramolecular ene-yne metathesis / [2,3]-rearrangement.

These examples illustrate the potential for oxonium ylide-mediated processes in synthesis. The factors of ylide ring size and ether substitution have been explained to demonstrate the possible carbocyclic frameworks that are accessible through these methodologies. Furthermore, the additional possibilities of ylide rearrangements based on variation in catalyst have been shown to provide products of notable interest. The results thus far have been based on the simplest cases of monocyclic oxonium ylides. Additional molecular complexity can be added to the products of this process by generating bicyclic oxonium ylides.

1.5. The Synthesis of Bicyclic Oxonium Ylides

When the ethereal oxygen to undergo oxonium ylide formation is already part of a ring, the oxonium ylide is bicyclic with the oxonium ion at a bridgehead of the bicycle. Bicyclic ylides tend to decompose via four distinct pathways (Figure 1.14) and the products that can result upon ylide formation are many:

a: endocyclic [1,2]-shift of a stabilized carbon

b: exocyclic [1,2]-shift of a stabilized carbon

c: α',β-fragmentation with C-O bond cleavage

d: ylide reversion then C-H insertion

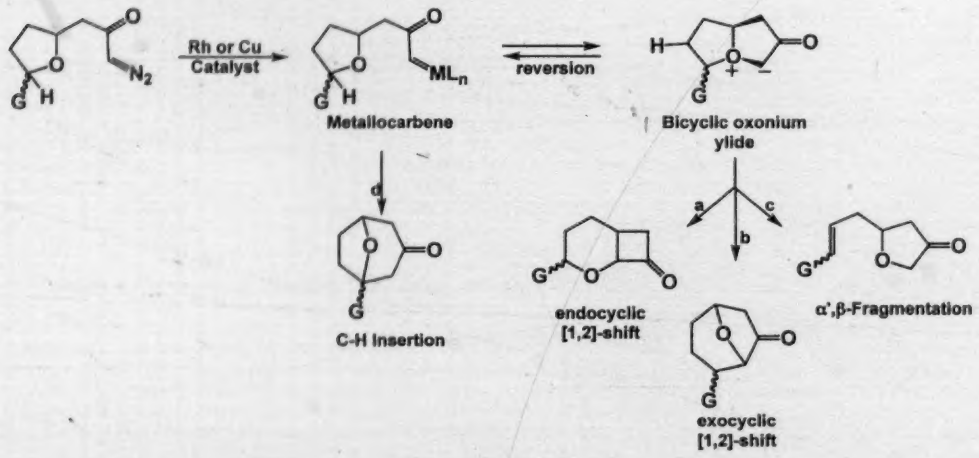
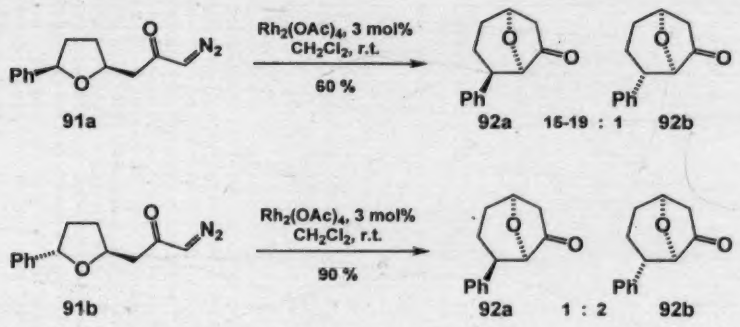


Figure 1.14: The reactive pathways typically undergone by bicyclic oxonium ylides.

1.5.1. THP and THF Derived Oxonium Ylides

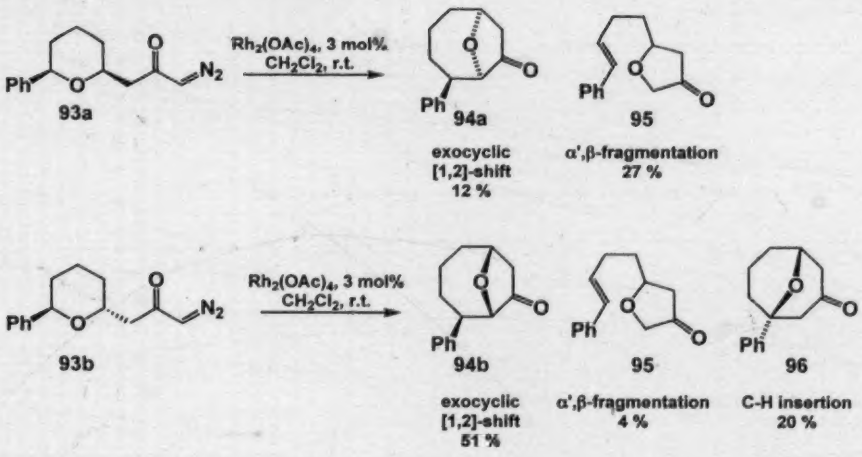
In an early example, West and co-workers[35] showed that simple diazoketone-substituted tetrahydrofuran (THF) substrates could easily undergo exocyclic [1,2]-shifts of suitably stabilized carbons (Scheme 1.29).



Scheme 1.29: The exocyclic benzyl [1,2]-shift of diazoketone-substituted THFs.

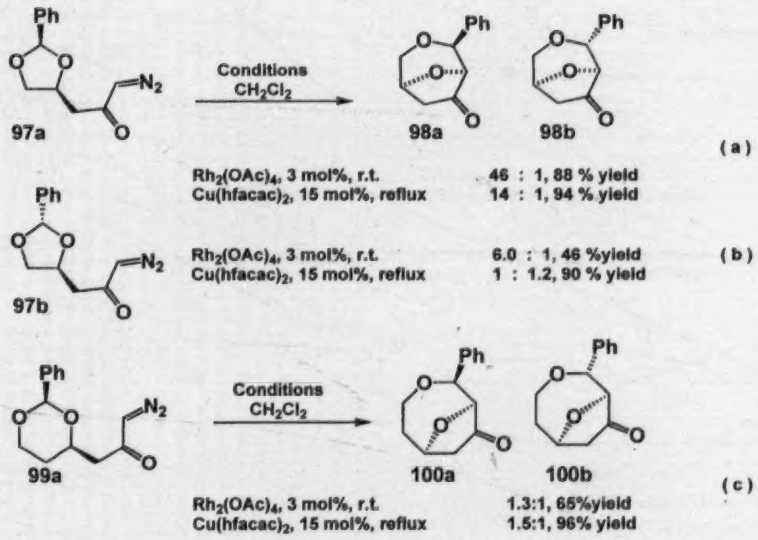
The exocyclic [1,2]-shift of **91a** affords the products **92a,b** in good to excellent yield under rhodium catalysis, and the migration occurs predominantly with retention of configuration of the stereogenic centre. Based on the biradical intermediate proposed for the [1,2]-shift, it appears that radical recombination for the *cis* substituted THP is faster than that for the *trans* substituted THP, affording the product with a greater degree of retention of configuration.

West extended this to the tetrahydropyran (THP) substrates wherein they observed that the exocyclic [1,2]-shift afforded products **94a,b** with complete retention of configuration of the migrating centre (Scheme 1.30). Unfortunately, numerous other side products derived from α',β-fragmentation (**95**) and C-H insertion (**96**) were also observed. These results indicate that the exocyclic [1,2]-shift is a feasible entry into oxygen-bridged 7-membered rings, but that the chemoselectivity of the process decreases as the size of the bicyclic oxonium ylide increases.



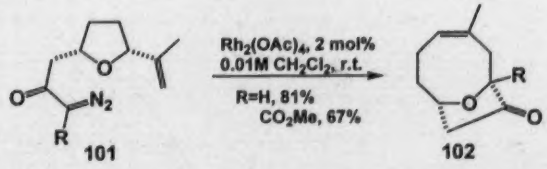
Scheme 1.30: The exocyclic benzyl [1,2]-shift of diazoketone-substituted THPs.

West has further shown that by changing the connectivity of the starting ketal, one can promote an oxygen-stabilized exocyclic [1,2]-shift to afford oxygen-bridged heterocycles (Scheme 1.31).[43] They showed that for the dioxabicyclo-[3.3.0]octane ylide generated from **97a**, the [1,2]-shift occurred, giving **98a,b** with near complete retention of configuration at the migrating centre (eq. a). Interestingly, treatment of **97b** with $Rh(OAc)_4$ afforded **98a** as the major product whereas $Cu(hfacac)_2$ afforded the product **98b** as the slightly major isomer (eq. b). The study was extended to the dioxane **99a** which underwent the exocyclic [1,2]-shift affording products **100a,b** as a mixture in which the product of migration with retention was the major isomer (**100b**) (eq. c). These results demonstrate another oxygen-bridged heterocyclic framework that can be obtained as a result of the rearrangements associated with oxonium ylides generating bridged medium-sized rings in high yield.



Scheme 1.31: Acetal-derived oxygen-bridged heterocycles.

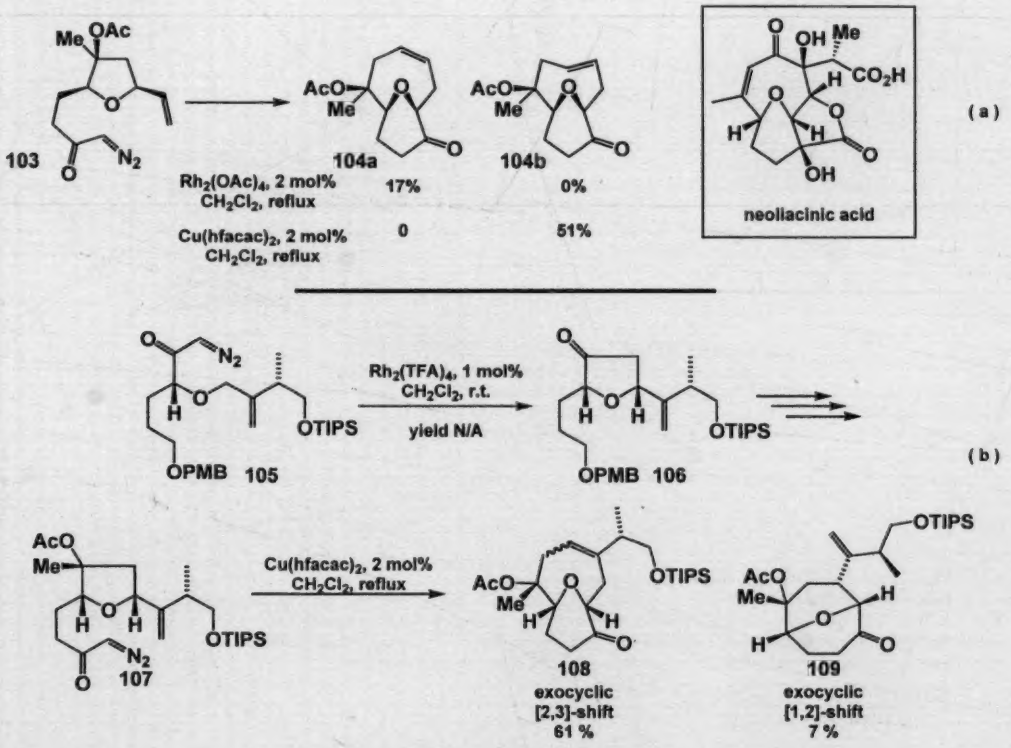
There have also been several examples in the use of vinyl-substituted tetrahydrofurans and tetrahydropyrans to effect ring enlargement based on the original example of Pirrung[20] (Scheme 1.32). He showed that the formation of an oxonium ylide with a vinyl-substituted tetrahydrofuran (**101**) afforded a ring-expanded oxa-bridged bicycle upon [2,3]-shift.



Scheme 1.32: Ring expansion through [2,3]-shift of a vinyl-substituted THF.

Clark[44] showed that a functionalized homologue of **101**, substrate **103**, could also undergo ring-expansion, though in lesser yield using rhodium catalysis (Scheme 1.33). Clark also attempted the $Cu(hfacac)_2$ catalyzed reaction which gave **104b** in 51 % yield as the *trans* olefin, which could be isomerized to the *cis* olefin **104a** in 90 % yield. This

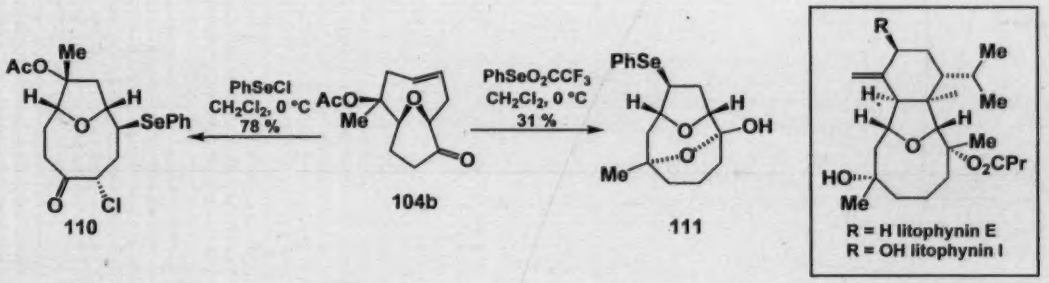
investigation served as a model study for the synthesis of the bicyclic core of neoliacinic acid. In the advanced synthesis of the functionalized core, Clark built the rearrangement precursor using a carbenoid C-H insertion followed by the tandem ylide formation and rearrangement protocol (Scheme 1.33, eq. b).[45] A derivative of commercially available (*R*)-3-hydroxy-2-methylpropionate was coupled with a derivative of (*R*)-isopropylideneglyceraldehyde affording, after several manipulations, C-H insertion precursor **105**. This underwent C-H insertion to give **106** as a ~7:1 ratio favoring the *trans* isomer. Upon conversion to the rearrangement precursor **107**, treatment with $Cu(hfacac)_2$ afforded **108** in 61 % yield as a mixture of *Z* and *E* isomers, as well as 7 % of **109**, the product of the vinyl-stabilized [1,2]-shift.



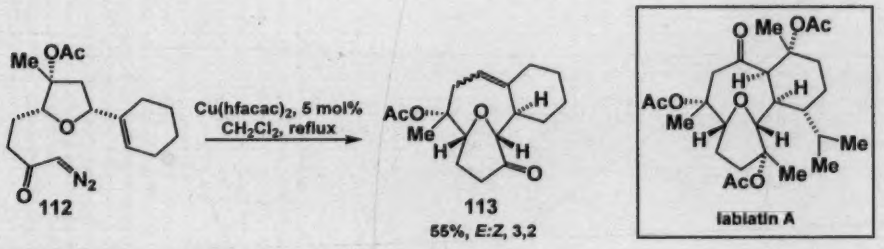
Scheme 1.33: Model study and the synthesis of the core of neoliacinic acid.

In subsequent manipulations of the neoliacinic acid core, Clark has shown that intermediate **104b** can be treated with electrophilic selenides to effect structural

rearrangements that result in carbocycles having the core structure of the litophinins E and I (Scheme 1.34).[46] By incorporating the vinyl group into a cyclohexene unit, this methodology has also been used by Clark to afford the tricyclic core of labiatin A (Scheme 1.35).[40] These examples by Clark demonstrate that the use of an oxonium ylide-mediated ring enlargement in synthesis is feasible in a moderately functionalized molecule and that the carbocyclic frameworks of various natural products are attainable in relatively few synthetic operations.



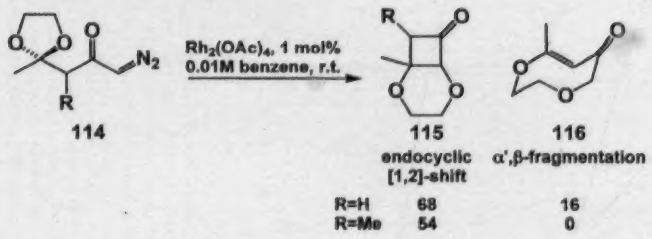
Scheme 1.34: Synthesis towards the core of litophynin E and I.



Scheme 1.35: Synthesis towards the core of labiatin A.

1.5.2. Oxonium Ylides Generated from Ketals

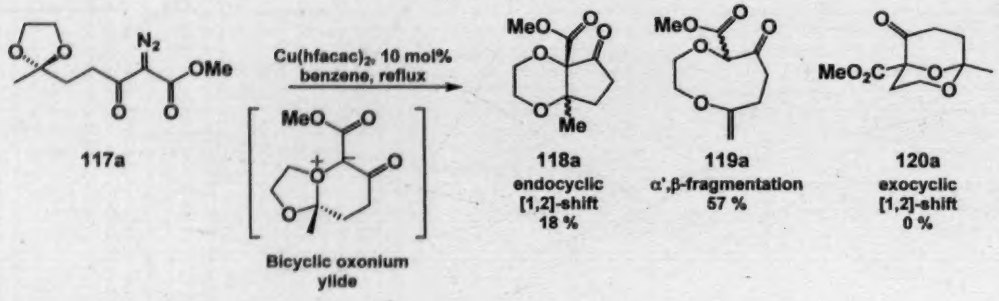
Johnson showed that the formation of an oxonium ylide with a ketal oxygen affords the products of both the endocyclic [1,2]-shift (**115**) and the α',β-fragmentation pathway, **116** (Scheme 1.36).[21]



Scheme 1.36: Rearrangement and fragmentation pathways of a bicyclic oxonium ylide.

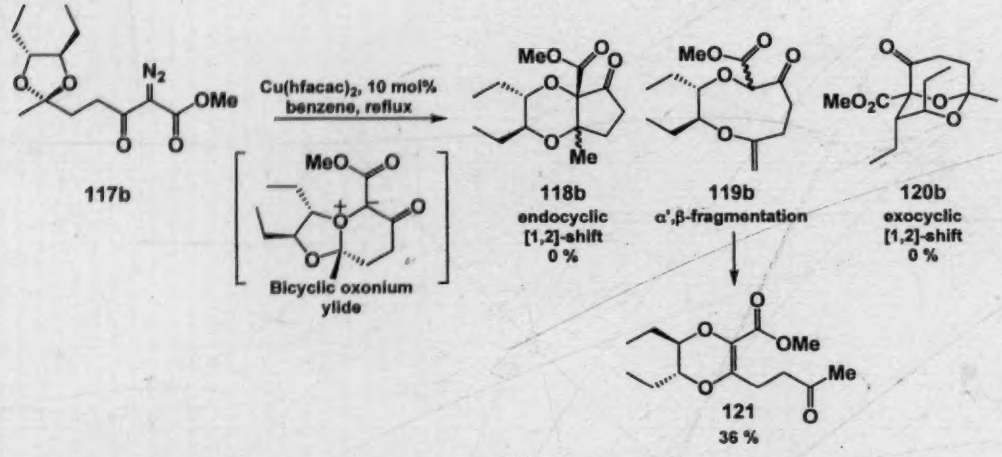
Examples of rearrangements from acetal and ketal-derived oxonium ylides have shown that multiple reactive pathways may be operative in a given system.[47] While the stabilization gained by oxygen-substitution is sufficient to promote the [1,2]-shift, there are other factors that can affect the course of the reaction. These include ring size of the bicyclic ylide, stabilizing groups appropriately situated elsewhere on the bicyclic ylide, as well as additives in the reaction mixture. These factors can all affect the course of a reaction, and will be examined on a case-by-case basis.

Zercher[48,49] investigated the factors that influence ylide formation with ketal oxygens, and the subsequent reactivities of these ylides, by preparing a series of differentially-substituted dioxolanes. Zercher initially tested substrate **117a** which would make a dioxabicyclo[4.3.0]nonane oxonium ylide. Treatment of this with $Cu(hfacac)_2$ afforded 18 % of the [1,2]-shift product **118a** and 57 % of the α',β-fragmentation product **119a** (Scheme 1.37). Interestingly, a secondary attempt at this reaction using anhydrous $Cu(hfacac)_2$ afforded only the [1,2]-shift product in 51 % yield. It was proposed the water from the catalyst hydrate acted as a base, which enabled the formation of **119a**. Comparing this result to that of Johnson, it appears that the increased size of the bicyclic ylide (oxoniabicyclo[3.3.0] vs [3.4.0]) has little effect on the endocyclic [1,2]-shift.



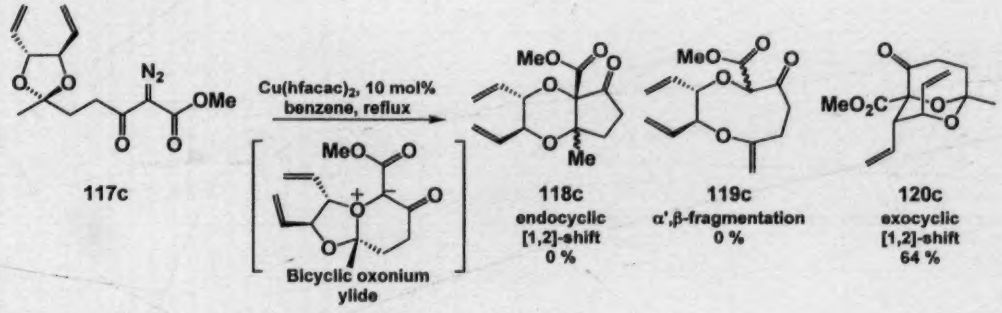
Scheme 1.37: The endocyclic [1,2]-shift of an unsubstituted dioxolane.

As was shown by Johnson, [1,2]-shifts that proceed through alkyl stabilized radical intermediates are unproductive, and the oxonium ylides will typically decompose by alternative, lower energy, reactive pathways (Scheme 1.4, eq. c). Continuing with the dioxolane study, Zercher attempted to promote the exocyclic [1,2]-shift with the diethyl-substituted dioxolane **117b** (Scheme 1.38). Isolated product **121** was derived from the α',β-fragmentation pathway, with no observation of either of the [1,2]-shift products **118b** or **120b**.



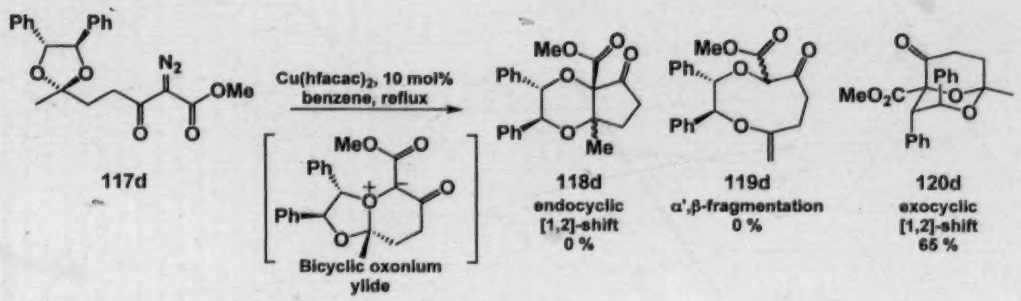
Scheme 1.38: The attempted [1,2]-shift of a diethyl-substituted dioxolane.

Zercher subsequently investigated **117c**, and likely expected that this vinyl substitution might enable a low-energy [2,3]-rearrangement by which the oxonium ylide could decompose (Scheme 1.39). The observed product **120c** was the result of an exocyclic shift, with none of the α',β-fragmentation product **119c** or the endocyclic [1,2]-shift product **118c**. Analysis showed it to have come from a vinyl-stabilized [1,2]-shift, and not [2,3]-rearrangement.



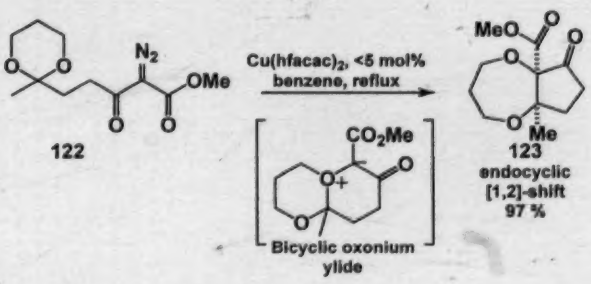
Scheme 1.39: The vinyl-stabilized exocyclic [1,2]-shift.

The lack of a [2,3]-shift product could be another example of an ylide whose rigid structure confines the vinyl terminus outside the bonding proximity, inhibiting the rearrangement.[41] This result offered clear evidence that exocyclic [1,2]-shifts are possible if sufficient stabilization is present, favored even when there is an oxygen-stabilized endocyclic [1,2]-shift possible. This may be explained by a vinyl group of an allyl radical being better at stabilizing the radical intermediate than the alternative oxygen-substituted radical needed for the endocyclic [1,2]-shift. It may also be that the endocyclic [1,2]-shift is a higher energy molecular reorganization than the exocyclic [1,2]-shift, so that when sufficient stabilization is available, the dominant process would be the exocyclic shift. In line with this proposal, the additional substrate **117d**, having a diphenyl-substituted dioxolane, was tested and again afforded the product of the exocyclic [1,2]-shift **120d** in 65% (Scheme 1.40).



Scheme 1.40: The benzyl-stabilized exocyclic [1,2]-shift.

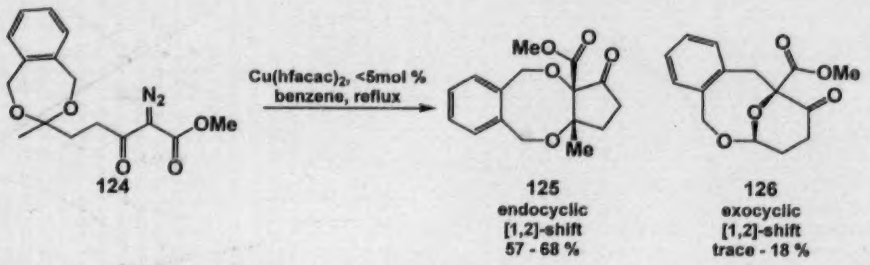
Subsequent experiments investigated the effects of oxonium ylide ring size on these rearrangements. The dioxane substrate **122** afforded product **123** of the endocyclic [1,2]-shift in quantitative yield upon ylide formation (Scheme 1.41). There is no stabilization on the dioxane carbons for the exocyclic rearrangement to occur and, furthermore, it may be that this ring size is sufficiently large that the fragmentation pathway is no longer operative. As well, the increase in overall yield indicates that the increase in ring size may facilitate the endocyclic [1,2]-shift.



Scheme 1.41: The endocyclic [1,2]-shift of an unsubstituted dioxane

Zercher sought to test this notion through the reaction of substrate **124**. It was imagined that the larger ring size would encounter little resistance to the oxygen-stabilized endocyclic [1,2]-shift, and benzyl-substitution would facilitate the exocyclic [1,2]-shift. Upon treatment of **124** with $Cu(hfacac)_2$, products **125** and **126** resulted, under varying reaction conditions, affording **125** as the major product in all cases

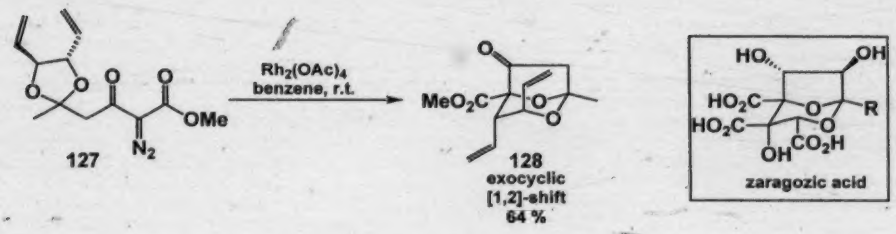
(Scheme 1.42). However, this may also be a factor of the forming benzylic radical not being stabilized by the aromatic ring in the transition state, because the bond undergoing homolysis is orthogonal to the pi-system (See also Scheme 1.15, Scheme 1.20)



Scheme 1.42: Competition study between the endo- and exocyclic [1,2]-shifts of a ketal-derived oxonium ylide.

The authors suggested that benzylic stabilization was not the dominant factor in determining the course of the reaction upon ylide formation. It appears that oxygen-substitution is better at promoting bond homolysis, and that the earlier results where the exocyclic [1,2]-shift is the dominant process could be the result of geometric or strain considerations. The results of Zercher's investigation showed a trend that larger ketal ring size facilitates the endocyclic [1,2]-shift, and that smaller-sized oxonium ylide substrates will react by other pathways, such as the α',β-fragmentation or exocyclic [1,2]-shift (when substituted with sufficient stabilizing groups).

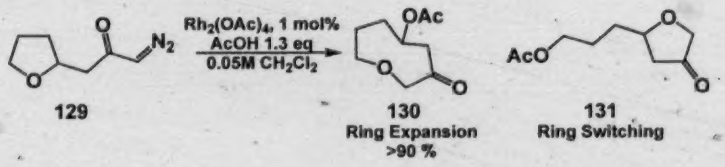
While Johnson showed that the oxoniabicyclo[3.3.0]octane ylide would react by either the fragmentation or the endocyclic [1,2]-shift (Scheme 1.36), Zercher envisioned that by substituting the dioxolane with allyl-stabilizing groups he could promote the exocyclic [1,2]-shift (Scheme 1.43). In the event, treatment of **127** with $Rh_2(OAc)_4$ afforded the desired product **128** in 64 % yield, providing an efficient entry into the core tricyclic structure of zaragozic acid.[50] This is also an additional result that suggests the exocyclic shift is favored for appropriately-substituted smaller bicyclic ylides.



Scheme 1.43: Towards the core of zaragozic acid.

1.5.3. Oxonium Ylides for Ring Expansion

Oku and co-workers sought to exploit the inherent ring strain associated with the formation of a bicyclic oxonium ylide so as to generate large-size keto ethers through a ring expansion / fragmentation protocol. As shown by Johnson[21] and Zercher[48, 49] when small, bicyclic oxonium ylides are formed, the endocyclic [1,2]-shift suffers from competition with other reactive pathways, such as the α',β-fragmentation. Oku envisioned the use of additives to promote this other pathway, similar to that seen by Zercher when using the hydrate of $Cu(hfacac)_2$ (Scheme 36). Treatment of diazoketone-substituted heterocycle **129** with $Rh_2(OAc)_4$ in the presence of additives afforded the desired ring-expanded products **130** in >90 % yield (Scheme 1.44).[51]



Scheme 1.44: The ring expansion of a bicyclic oxonium ylide.

In the proposed mechanism,[51] the initially-formed metallocarbene underwent oxonium ylide formation (Figure 1.15). If this is not feasible (due to larger ring size), the metallocarbene may then undergo O-H insertion (Figure 14, path a). If ylide formation is facile, but the nucleophile is not sufficiently acidic, the [3+2] cycloreversion is observed, giving product **132** (Figure 1.15, path c). If the ylide is protonated to generate an

oxonium ion (path b), it may undergo attack by the conjugate base of the additive to afford the ring-expanded products **130a,b** (Figure 1.15, path b). The ring-switched product **131** may also result when there is insufficient ring strain to promote for ring opening. It was observed that additives of increased pKa, whose ability to protonate the oxonium ylide would be diminished, gave lower yields of the ring-expanded product. For example, the yield of ring-expanded products dropped from >90 % (acetic acid) to 61 % (phenol) or 5 % (trifluoroethanol). Studies on substrates with increasing ketal ring size values (n = 2-4) were successful in the presence of acetic acid, the product being obtained in ~75 % in all cases. The limitation of this protocol was found to be cases where the value of m>1. As the length of the diazoketone tether increased, the predominant product was either a result of ring-switching or cycloreversion. In a separate investigation, Oku showed they could increase the yield of products from the cycloreversion pathway by conducting the carbene transfer in the presence of methanol, which afforded the products in good to excellent yield.[52]

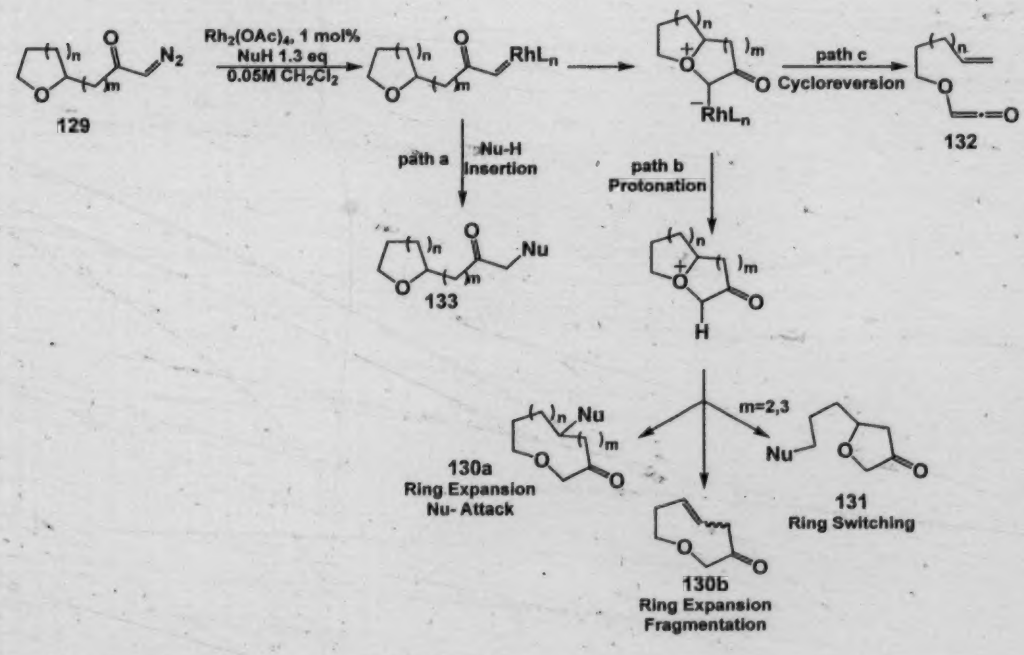


Figure 1.15: The mechanism of the Oku Process.

The authors believed the inability of larger bicyclic oxonium ylides to undergo ring expansion resulted from a decrease in ring strain as the size of the bicyclic ylide increased. A subsequent survey of ylides formed in the presence of nucleophiles showed that only the oxoniabicyclo[3.3.0]octane ylide possessed enough ring strain to spontaneously undergo ring-expansion by nucleophilic attack.[53] These observations proved to be a limitation in the further development of the diazoketone branched tetrahydrofuran protocol. However, Oku presumed that if a cation-stabilizing group were placed adjacent to the bridgehead carbon of the ylide it would facilitate, if not promote ring expansion (Figure 1.16).

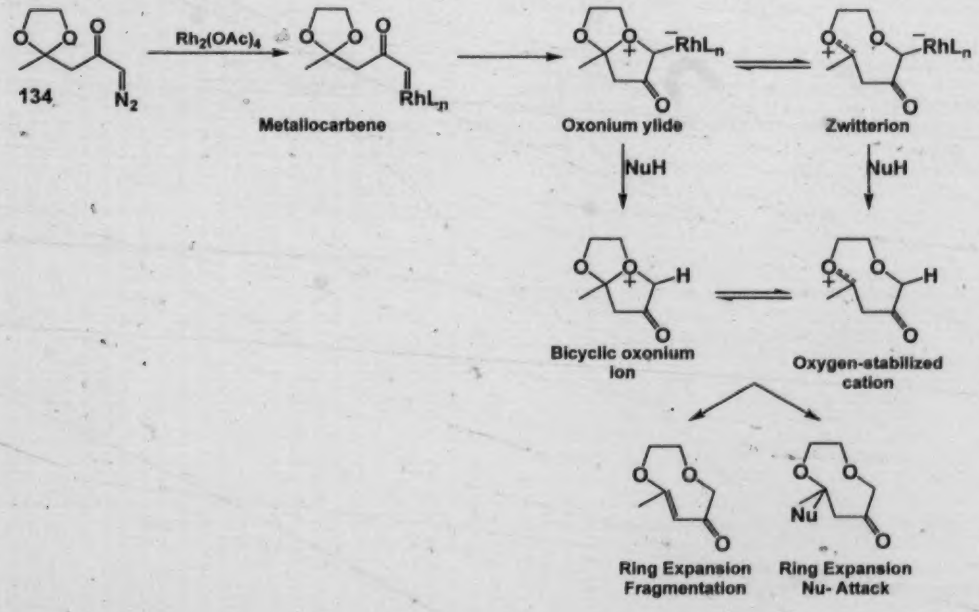
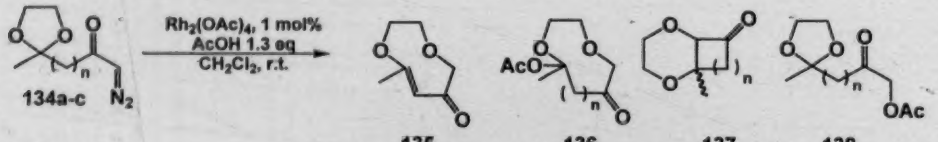


Figure 1.16: The reactive pathway of an oxygen-assisted ring opening.

The examples of Johnson and Zercher served as precedent, showing the internal bond of a ketal-derived oxonium ylide could be cleaved when no low-energy pathway was available. As before, Oku envisioned the [1,2]-shift would be suppressed if the intermediate oxonium ylide were protonated by an acidic additive, making it susceptible to attack thereafter by the resulting conjugate base. Indeed, when dioxa-

bicyclo[3.3.0]octane ylide was generated from **134a** under rhodium catalysis, the products of ring expansion (both nucleophilic attack and α',β-fragmentation) were recovered in 87 % yield (Scheme 1.45). Oku then proceeded to test **134b** (n = 2), from which the ring expanded products were isolated in 67 % yield, as well as 6 % of the O-H insertion product. This showed that ring cleavage was facilitated by the stabilization gained upon oxygen substitution, which enabled a ring expansion found to be ineffective in the tetrahydrofuran protocol. Oku subsequently found that the ring expansion of **134c** failed to occur, affording instead the endocyclic [1,2]-shift and the O-H insertion product (Scheme 1.45). To extend the versatility of this new method, Oku also investigated the effect of varying the ketal ring size and found this was still moderately effective, but increasing the tether length resulted in a decreased yield of the ring expansion products.



	n	135 Ring Expansion Fragmentation	136 Ring Expansion Nu- Attack	137 Endocyclic [1,2]-shift	138 O-H Insertion
134a	1	46	41	-	-
134b	2	-	67	-	6
134c	3	-	-	24	41

Scheme 1.45: Ring expansion of dioxolane-derived oxonium ylides.

Because stabilization of the zwitterion is gained through increased oxygenation at the carbocation center of the ring expansion intermediate, Oku subsequently developed a series of ortho ester substituted diazoketone substrates **139** (Figure 1.17) believing the ring opening the of tricyclic oxonium ylide to the zwitterion would be further facilitated.[54] Treatment of **139a**, where n = 1, with $Rh_2(OAc)_4$ afforded quantitatively the ring expansion product, similar to the reaction of **139b**, where n = 2, which afforded 81 % of the ring expanded product as well as 9 % of the OH insertion product. Conversely, substrate **139c**, n = 3, afforded 28 % of the insertion product, and 34 % of the [1,2]-product (none of the ring expanded product was observed) upon treatment with $Rh_2(OAc)_4$. Though this novel protocol enabled the ring expansion on ylides of an

incrementally larger ring size, it still held that the occurrence of the ring-expanded product decreased as the O-H insertion and endocyclic [1,2]-shift pathways became more competitive.

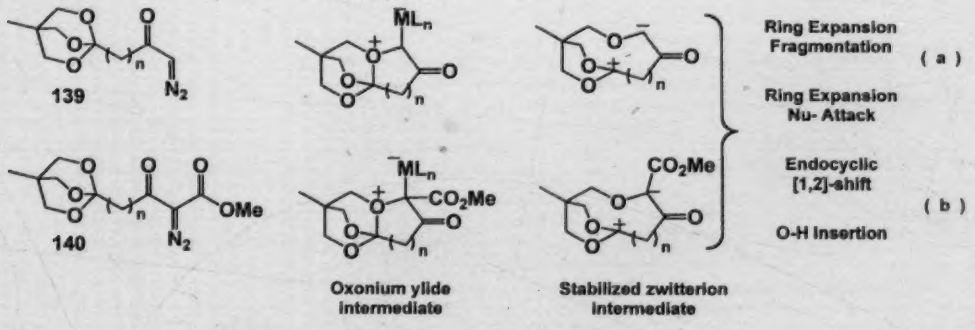
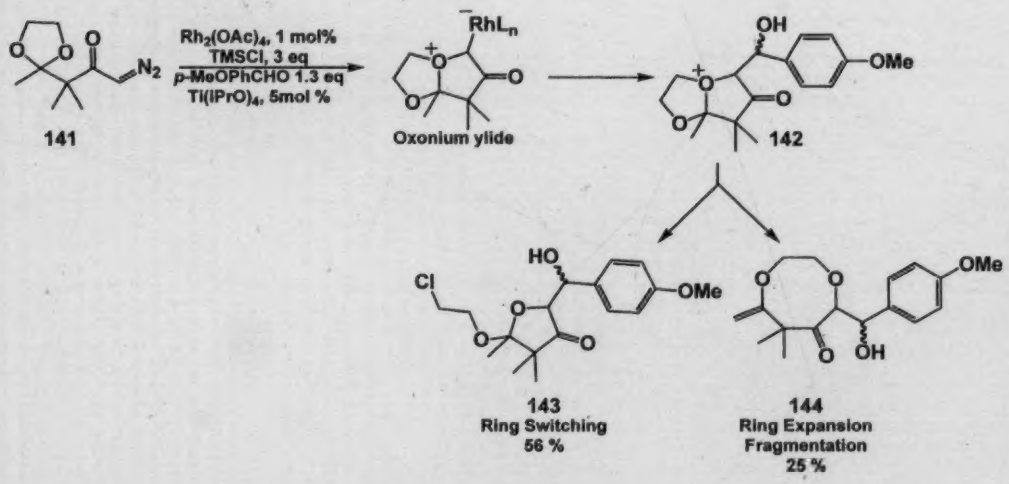


Figure 1.17: The ortho ester substrates tested by Oku, as well as the carbomethoxy-substituted substrates to provide anion stabilization.

As a final investigation into the factors influencing the ring expansion mechanism, Oku prepared a series of carbomethoxy-substituted ortho ester substrates **140** that would also stabilize the anionic charge of the ylide or zwitterion through delocalization. It was found for smaller ring sizes that the ring-expanded products are isolated in quantitative NMR yields, and as ring size increases the chemoselectivity does not decrease as dramatically as seen with previous scaffolds. In accordance with their hypothesis, it was the additional stabilization afforded the zwitterionic intermediates that led to the ring expansion of even larger bicyclic oxonium ylides.

In analogy to the proton-based ylide trapping, Oku also envisioned using other electrophilic trapping agents to suppress the endocyclic Stevens [1,2]-shift pathway, and promote ring expansion. He tested a host of trialkylsilyl chloride reagents and found that TMSCl was highly effective toward this end.[55] They determined that the reaction proceeded by formation, and subsequent hydrolysis, of a silyl enol ether, which led Oku to further devise a method in which the silyl enol ether could be used for a synthetic purpose. He demonstrated that the silyl enol ether could be used to react with a carbonyl-

based electrophile to afford the aldol-like products in the course of the ring expansion process (Scheme 1.46).[56,57] As an example, he showed that the aldol-derived products **143** and **144** could be isolated in 81 % yield. This product mixture consisted of 25 % of the subsequently ring-expanded product **144** and 56 % of the post-aldol ring-switched product **143**.



Scheme 1.46: The oxonium ylide / aldol trapping reaction.

1.6. Conclusions

The results presented herein have highlighted the reactivities of oxonium ylides. These intermediates are most efficiently generated through the transition metal-catalyzed carbene transfer of diazoketones, and subsequent intramolecular attack of a pendant oxygen. Ether, acetal and ketal oxygens all readily form oxonium ylides. It was commonly observed that there is a kinetic preference for 5-membered oxonium ylide formation. In substrates where this was not feasible, it was shown that changing to more electrophilic catalysts can enable the formation of larger cyclic ylides.

There are several reactive pathways available by which oxonium ylides tend to decompose. When appropriately substituted, these ylides will rearrange by either [1,2]- or [2,3]- shifts. The [2,3]-sigmatropic rearrangement has been shown to be a favorable process for allyl or propargyl-substituted ethers. The Stevens [1,2]-shift of monocyclic oxonium ylides occurs typically with benzyl or heteroatom substitution, as both of these groups have been found to effectively stabilize the putative biradical intermediate of the [1,2]-shift. In competition studies, heteroatom stabilization was found to be a dominant factor deciding the course of the [1,2]-shift. When a rearrangement pathway is unavailable (or suppressed), oxonium ylides can either undergo fragmentation or reversion to the metallocarbene.

Bicyclic oxonium ylides of acetals or ketals were shown to decompose by various reactive pathways. Most commonly observed was the endocyclic [1,2]-shift of an oxygen-substituted, carbon centered radical, especially upon formation of larger oxoniabicyclic ylides. Smaller bicyclic ylides tend to undergo the exocyclic [1,2]-shift of benzyl or allyl substituted ethers, as these are effective at stabilizing the intermediate radical through conjugation. When such substitution was not available, these smaller ylides tended to decompose through ring expansion. By adding acidic nucleophiles to the reactions of larger oxoniabicyclic ylides, the competing endocyclic [1,2]-shift can be suppressed in favor of the ring expansion pathway, though this is only moderately effective. However, it was shown by increasing the stabilization of the intermediate ylide (by either increased oxygenation or anion stabilization), the ring expansion of increasingly larger oxoniabicyclic ylides is enabled.

The various reactive pathways of oxonium ylides have been shown to afford numerous structural motifs including furan-3-ones and pyran-3-ones as well as medium-sized and oxygen-bridged carbocycles. There were limited examples of employing substrates with additional fused rings affording fused, bicyclic products. Examples of the use of heteroatom stabilization in the exocyclic [1,2]-shift were lacking, even though heteroatoms were found to be dominant stabilizing groups. In Chapter 2, our efforts toward the heteroatom-stabilized exocyclic [1,2]-shift of mixed acetal-derived oxonium

ylides will be presented. These rearrangements have been shown to readily afford oxygen-bridged, fused medium-sized rings in good yield with high diastereoselectivity. The target structural motifs are common to various classes of natural products, and our efforts to apply this methodology toward the synthesis of of (+)-dactylol will be presented in Chapter 4.

1.6. References

1. Padwa, A.; Hornbuckle, S. F., Ylide Formation from the Reaction of Carbenes and Carbenoids with Heteroatom Lone Pairs. *Chem. Rev.* **1991**, 91, (3), 263-309.

2. Tomioka, H.; Kobayashi, N.; Murata, S.; Ohtawa, Y., Intervention of Carbonyl and Oxonium Ylides in Reactions of [(Alkoxycarbonyl)Phenyl]Carbenes in the Gas-Phase Forming 3-Alkylphthalides and 2-Alkoxy-1(2h)-Benzocyclobutenone - C-13 and O-18 Labeling Studies. *J. Am. Chem. Soc.* **1991,** 113, (23), 8771-8778.

3. Wolff, L.; Kruche, R., Uber Diazoanhydride (1,2,3-Oxydiazole Oder Diazoxyde) Und Diazoketone. *Liebigs Ann. Chem.* **1912,** 394, (1), 23-59.

4. Doyle, M. P.; Mckervey, M. A.; Ye, T., *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*. Wiley-Interscience: New York, 1997; p 652.

5. Cheng, J. P.; Liu, B.; Zhao, Y. Y.; Sun, Y. K.; Zhang, X. M.; Lu, Y., Effects of Adjacent Onium Cations and Remote Substituents on the H-A(+) Bond Equilibrium Acidities in Dimethyl Sulfoxide Solution. An Extensive Ylide Thermodynamic Stability Scale and Implication for the Importance of Resonance Effect on Ylide Stabilities. *J. Org. Chem.* **1999,** 64, (2), 604-610.

6. Olah, G. A.; Doggweiler, H.; Felberg, J. D., Onium Ylide Chemistry .2. Methylenedialkyloxonium Ylides. *J. Org. Chem.* **1984,** 49, (12), 2112-2116.

7. Olah, G. A.; Doggweiler, H.; Felberg, J. D., Onium Ylide Chemistry .3. Evidence for Competing Oxonium Ylide Formation with C-H Insertion in Meerwein's Reaction of Methylene and Methylene-D2 with Dialkyl Ethers. *J. Org. Chem.* **1984,** 49, (12), 2116-2120.

8. Olah, G. A.; Doggweiler, H.; Felberg, J. D.; Frohlich, S.; Grdina, M. J.; Karpeles, R.; Keumi, T.; Inaba, S.; Ip, W. M.; Lammertsma, K.; Salem, G.; Tabor, D. C., Onium Ylide Chemistry .1. Bifunctional Acid Base-Catalyzed Conversion of Heterosubstituted

Methanes into Ethylene and Derived Hydrocarbons - the Onium Ylide Mechanism of the C1-]C2 Conversion. *J. Am. Chem. Soc.* **1984,** 106, (7), 2143-2149.

9. Padwa, A.; Curtis, E. A., Generation of Carbonyl Ylide Dipoles from the Rh(II) - Catalyzed Cyclization of Alpha-Diazo-Beta-Keto-1,5-Diesters. *Arkivoc* **2001,** 2, 1043-1053.

10. Padwa, A.; Zhang, Z. J. J.; Zhi, L., Cyclization-Cycloaddition Cascade of Rhodium Carbenoids Using Different Carbonyl Groups. Highlighting the Position of Interaction. *J. Org. Chem.* **2000,** 65, (17), 5223-5232.

11. Nozaki, H.; Takaya, H.; Noyori, R., Reaction of Carbethoxycarbene with 2-Phenyloxirane and 2-Phenyloxetane. *Tetrahedron* **1966,** 22, (10), 3393-3401.

12. Nozaki, H.; Takaya, H.; Noyori, R., Reaction of Ethyl Diazoacetate with Styrene Oxide. *Tetrahedron Lett.* **1965**, (30), 2563-2567.

13. Friedrich, K.; Jansen, U.; Kirmse, W., Oxygen Ylides .1. Reactions of Carbenes with Oxetane. *Tetrahedron Lett.* **1985,** 26, (2), 193-196.

14. Kirmse, W.; Vanchiem, P.; Schurig, V., Oxygen Ylides .2. Photochemical and Rhodium-Catalyzed Reactions of Diazomethane with (S)-2-Methyloxetane. *Tetrahedron Lett.* **1985,** 26, (2), 197-200.

15. Adams, J.; Poupart, M. A.; Grenier, L.; Schaller, C.; Ouimet, N.; Frenette, R., Rhodium Acetate Catalyzes the Addition of Carbenoids Alpha-Oxygens to Ether Oxygens. *Tetrahedron Lett.* **1989,** 30, (14), 1749-1752.

16. Adams, J.; Spero, D. M., Rhodium (II) Catalyzed-Reactions of Diazo-Carbonyl Compounds. *Tetrahedron* **1991,** 47, (10-11), 1765-1808.

17. Taber, D. F.; Petty, E. H., General-Route to Highly Functionalized Cyclopentane Derivatives by Intramolecular C-H Insertion. *J. Org. Chem.* **1982,** 47, (24), 4808-4809.

18. Moyer, M. P.; Feldman, P. L.; Rapoport, H., Intramolecular N-H, O-H, and S-H Insertion Reactions. Synthesis of Heterocycles from α-Diazo-β-Keto Esters *J. Org. Chem.* **1985,** 50, (25), 5223-5230.

19. Thijs, L.; Zwanenburg, B., Oxygen-Transfer During the Copper Induced Reaction of Alpha,Beta-Epoxy Diazomethyl Ketones. *Tetrahedron* **1980,** 36, (14), 2145-2148.

20. Pirrung, M. C.; Werner, J. A., Intramolecular Generation and [2,3]-Sigmatropic Rearrangement of Oxonium Ylides. *J. Am. Chem. Soc.* **1986,** 108, (19), 6060-6062.

21. Roskamp, E. J.; Johnson, C. R., Generation and Rearrangements of Oxonium Ylides. *J. Am. Chem. Soc.* **1986,** 108, (19), 6062-6063.

22. Ollis, W. D.; Rey, M.; Sutherland, I. O., Base-Catalyzed Rearrangements Involving Ylide Intermediates .15. The Mechanism of the Stevens [1,2] Rearrangement. *J. Chem. Soc., Perkin Trans. 1* **1983,** (5), 1009-1027.

23. Karche, N. P.; Jachak, S. M.; Dhavale, D. D., Electronic Effects in Migratory Groups. [1,4]- Versus [1,2] -Rearrangement in Rhodium Carbenoid Generated Bicyclic Oxonium Ylides. *J. Org. Chem.* **2001,** 66, (19), 6323-6332.

24. Eberlein, T. H.; West, F. G.; Tester, R. W., The Stevens [1,2]-Shift of Oxonium Ylides - a Route to Substituted Tetrahydrofuranones. *J. Org. Chem.* **1992,** 57, (12), 3479-3482.

25. Pirrung, M. C.; Brown, W. L.; Rege, S.; Laughton, P., Total Synthesis of (+)-Griseofulvin. *J. Am. Chem. Soc.* **1991,** 113, (22), 8561-8562.

26. Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D., Reactivity Patterns in the Rhodium Carbenoid Induced Tandem Cyclization Cyclo-Addition Reaction. *J. Org. Chem.* **1989,** 54, (4), 817-824.

27. Marmsäter, F. P.; Vanecko, J. A.; West, F. G., Catalyst and Ring Size Effects on Periselectivity of Oxonium Ylide Rearrangements. *Org. Lett.* **2004,** 6, (10), 1657-1660.

28. Doyle, M. P.; Bagheri, V.; Claxton, E. E., Synthesis of Allenes by [2,3]-Sigmatropic Rearrangement of Prop-2-Yn-1-Yl Oxonium Ylides Formed in Rhodium(II) Carboxylate Catalyzed-Reactions of Diazo-Compounds. *J. Chem. Soc., Chem. Commun.* **1990**, (1), 46-48.

29. Clark, J. S., Diastereoselective Synthesis of 2,5-Dialkyl Tetrahydrofuran-3-Ones by a Copper-Catalyzed Tandem Carbenoid Insertion and Ylide Rearrangement Reaction. *Tetrahedron Lett.* **1992,** 33, (41), 6193-6196.

30. Clark, J. S.; Krowiak, S. A.; Street, L. J., Synthesis of Cyclic Ethers from Copper Carbenoids by Formation and Rearrangement of Oxonium Ylides. *Tetrahedron Lett.* **1993,** 34, (27), 4385-4388.

31. West, F. G.; Naidu, B. N.; Tester, R. W., Profound Catalyst Effects in the Generation and Reactivity of Carbenoid-Derived Cyclic Ylides. *J. Org. Chem.* **1994,** 59, (23), 6892-6894.

32. Nozaki, H.; Takaya, H.; Moriuti, S.; Noyori, R., Homogeneous Catalysis in Decomposition of Diazo Compounds by Copper Chelates. *Tetrahedron* **1968,** 24, (9), 3655-3669.

33. Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A., Catalytic Enantioselective Rearrangements and Cycloadditions Involving Ylides from Diazo Compounds. *Chem. Soc. Rev.* **2001,** 30, (1), 50-61.

34. Lambert, J. B.; Johnson, D. H., Stereochemistry and Inversion of Trivalent Oxygen. *J. Am. Chem. Soc.* **1968,** 90, (5), 1349-1350.

35. West, F. G.; Eberlein, T. H.; Tester, R. W., O-Bridged Medium-Sized Rings Via Bicyclic Oxonium Ylides. *J. Chem. Soc., Perkin Trans. 1* **1993,** (23), 2857-2859.

36. Clark, J. S.; Dossetter, A. G.; Whittingham, W. G., Stereoselective Synthesis of the Bicyclic Core Structure of the Highly Oxidised Sesquiterpene Neoliacinic Acid. *Tetrahedron Lett.* **1996,** 37, (31), 5605-5608.

37. Clark, J. S.; Fessard, T. C.; Whitlock, G. A., A Concise Enantioselective Synthesis of the Fungal Metabolite (+)-Decarestrictine L. *Tetrahedron* **2006,** 62, (1), 73-78.

38. Marmsäter, F. P.; West, F. G., Iterative Approach to Polycyclic Ethers Based on Stereoselective Oxonium Ylide [2,3]-Shifts. *J. Am. Chem. Soc.* **2001,** 123, (21), 5144-5145.

39. Clark, J. S.; Whitlock, G. A., A Short Synthesis of (+/-)-Decarestrictine-L. *Tetrahedron Lett.* **1994,** 35, (34), 6381-6382.

40. Clark, J. S.; Baxter, C. A.; Castro, J. L., Synthesis of the Tricyclic Core of the Marine Natural Product Labiatin A. *Synthesis-Stuttgart* **2005**, (19), 3398-3404.

41. Clark, J. S.; Walls, S. B.; Wilson, C.; East, S. P.; Drysdale, M. J., Construction of Fused Medium-Ring Carbocycles by Catalytic Generation and Rearrangement of Oxonium Ylides. *Eur. J. Org. Chem.* **2006**, (2), 323-327.

42. Padwa, A., Rhodium(II) Mediated Cyclizations of Diazo Alkynyl Ketones. *J. Organomet. Chem.* **2000,** 610, (1-2), 88-101.

43. Tester, R. W.; West, F. G., Medium Ring Ethers Via [1,2]-Shift of Acetal-Derived Oxonium Ylides. *Tetrahedron Lett.* **1998,** 39, (26), 4631-4634.

44. Clark, A. J.; Rooke, S.; Sparey, T. J.; Taylor, P. C., Synthesis of Styryl Tetrahydrofurans and Tetrahydropyrans Via Addition of Radicals to Unsaturated Sulfimides. *Tetrahedron Lett.* **1996,** 37, (6), 909-912.

45. Clark, J. S.; Dossetter, A. G.; Blake, A. J.; Li, W. S.; Whittingham, W. G., Synthesis of the Functionalised Core of Neoliacinic Acid. *Chem. Commun.* **1999**, (8), 749-750.

46. Clark, J. S.; Wong, Y. S., Construction of the 11-Oxabicyclo[6.2.1]Undecane Core of the Cladiellins by a Novel Rearrangement Reaction. *Chem. Commun.* **2000**, (12), 1079-1080.

47. Gutsche, C. D.; Hillman, M., Reactions of Ethyl Diazoacetate with Aromatic Compounds Containing Hetero Atoms Attached to the Benzyl Carbon. *J. Am. Chem. Soc.* **1954,** 76, (8), 2236-2240.

48. Brogan, J. B.; Bauer, C. B.; Rogers, R. D.; Zercher, C. K., Selectivity in the Rearrangements of Oxonium Ylides. *Tetrahedron Lett.* **1996,** 37, (29), 5053-5056.

49. Brogan, J. B.; Zercher, C. K.; Bauer, C. B.; Rogers, R. D., Study of the Rearrangements of Oxonium Ylides Generated from Ketals. *J. Org. Chem.* **1997,** 62, (12), 3902-3909.

50. Brogan, J. B.; Zercher, C. K., Preparation of the Zaragozic Acid Core through the Rearrangement of an Oxonium Ylide. *Tetrahedron Lett.* **1998,** 39, (13), 1691-1694.

51. Oku, A.; Ohki, S.; Yoshida, T.; Kimura, K., Three-Carbon Ring-Enlargement of Ethereal Oxonium Ylides - a Viable Synthesis of Medium-Sized Cyclic Ketoethers. *Chem. Commun.* **1996,** (9), 1077-1078.

52. Oku, A.; Sawada, Y.; Schroeder, M.; Higashikubo, I.; Yoshida, T.; Ohki, S., [3+2] Cycloreversion of Bicyclo[M.3.0]Alkan-3-on-2-Yl-1-Oxonium Ylides to Alkenyloxyketenes. Stereospecific Aspect. *J. Org. Chem.* **2004,** 69, (4), 1331-1336.

53. Kamada, T.; Geqing; Abe, M.; Oku, A., Selectivity in the Ring-Expansion and Ring-Switching Reactions of Bicyclooxonium Ions. *J. Chem. Soc., Perkin Trans. 1* **1996,** (5), 413-416.

54. Oku, A.; Numata, M., Three- to Six-Carbon Ring-Enlargement Reaction of Cyclic Ortho Esters Bearing a Diazocarbonyl Side Chain. Use of the Intramolecular Formation of Tricyclooxonium Ylides. *J. Org. Chem.* **2000,** 65, (7), 1899-1906.

55. Mori, T.; Oku, A., Catalysis of Chlorosilane on the Ring-Expansion of Cyclic Acetals Bearing a Carbene Precursor. Lewis Acid-Base Effect on the Oxonium Ylide Intermediate. *Chem. Commun.* **1999,** (14), 1339-1340.

56. Sawada, Y.; Mori, T.; Oku, A., Aldol-Type Carbon Bond Formation of Ethereal Oxonium Ylide. *Chem. Commun.* **2001**, (12), 1086-1087.

57. Sawada, Y.; Mori, T.; Oku, A., Carbon-Carbon Bond Formation Reaction of Ethereal Oxonium Ylides Via Metal-Enolate Intermediates. *J. Org. Chem.* **2003,** 68, (26), 10040-10045.

2. Chapter 2

The Synthesis of Fused Carbocycles by the [1,2]-shift of Heteroatom-Stabilized Onium Ylides

2.1. Introduction

Fused polycycles are an integral part of the carbocyclic framework of many natural products. Hence, the stereocontrolled synthesis of fused rings, especially those that contain medium-sized (7-12 membered) rings, is an important challenge in organic synthesis. The occurrence of 7- and 8-membered rings is especially common in the realm of terpenoid chemistry, where there are many known natural products containing this structural motif. Another feature commonly observed is that the medium-sized rings are fused to one (or more) smaller rings, and in certain cases, there is oxygenation at the bridgehead carbon. Examples of these are (+)-dactylol, phorbol and prostratin (Figure 2.1). There are a number of approaches that have been developed for the synthesis of the 8-membered ring including cyclizations, cycloadditions and rearrangements.[1] One such approach involves the synthesis of a bridged bicyclic structure, which would reveal the bridgehead oxygenation upon cleavage of the bridge.[2-8] However, the cleavage of either an oxygen[9, 10] or carbon[11] bridge was found to be a difficult undertaking.

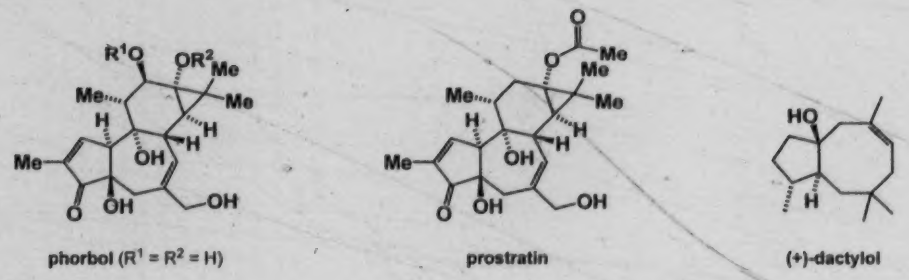


Figure 2.1: Examples of fused 5-7 and 5-8 bicycles with bridgehead oxygenation.

In the development of methods employing oxonium ylides for the synthesis of carbocycles, the West group has shown that oxygen-bridged medium-sized rings can be prepared in a few steps from readily available starting materials.[12, 13] One example employed the Stevens [1,2]-shift of ylides derived from 2-phenyl-tetrahydrofurans and pyrans with pendant diazoketones (Figure 2.2, eq. a).[13] While this proved another method by which the oxygen-bridged medium-sized rings could be prepared, the remote phenyl substituent is not synthetically versatile for subsequent operations. It was shown in Chapter 1 that heteroatoms are highly effective stabilizing groups for the Stevens [1,2]-shift. In modifying the original West substrate to include a heteroatom stabilizing group, the rearrangement becomes the Stevens [1,2]-shift of a mixed acetal- or thioacetal-derived oxonium ylide (Figure 2.2, eq. b). In choosing an appropriate stabilizing group, one having a variety of associated chemistries (such as a sulfide), it might be possible to promote cleavage of the bridging ether following the [1,2]-shift step. In this chapter, the development of the Stevens [1,2]-shift of fused, bicyclic mixed acetal- and thioacetal-derived oxonium ylides is presented, as well as the use of the remote sulfide functionality to enable the highly efficient cleavage of the bridging ether.

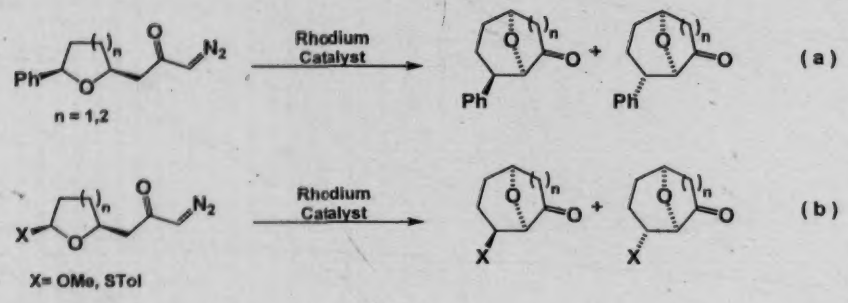


Figure 2.2: Substrates for heteroatom-stabilized exocyclic [1,2]-shifts, by analogy.

2.2. Background

The chemistry associated with catalytically generated oxonium ylides was shown in Chapter 1 to be readily applicable to the synthesis of small- and medium-sized rings. These carbocycles were generated through various rearrangements, such as the endocyclic [2,3]-shift, the exocyclic Stevens [1,2]-shift,[12, 13] as well as the internal α',β-fragmentation.[14, 15] In all of these cases, the intramolecular oxonium ylide formation occurred to give a bicyclic ylide. It has also been shown that fusing another ring to the scaffold affords a fused bicyclic product upon rearrangement.[16] These precedents indicated that the rearrangement would occur to afford medium-sized, fused bicyclic rings, and that the rearrangements would not be hampered by fusing another small ring to the scaffold.

The Oku,[14, 15] Johnson[17] and Zercher[18, 19] groups have all shown that the internal carbon of acetal- or ketal-derived oxonium ylides can readily undergo the [1,2]-shift. Though all of the examples covered in Chapter 1 were for shifts of oxygen-stabilized acetal or ketal carbons, it was believed that sulfides would also be as effective, if not more so, as stabilizing groups in the Stevens shift. In combining the structural features necessary to undertake the investigation, the substrate required would be a mixed (thio)acetal fused with a smaller ring, and having a pendant diazoketone. Through variation of the size of the fused ring, the size of the mixed acetal and the length of the

diazoketone tether, a wide variety of oxygen-bridged fused bicycles should be available via this approach (Figure 2.3).

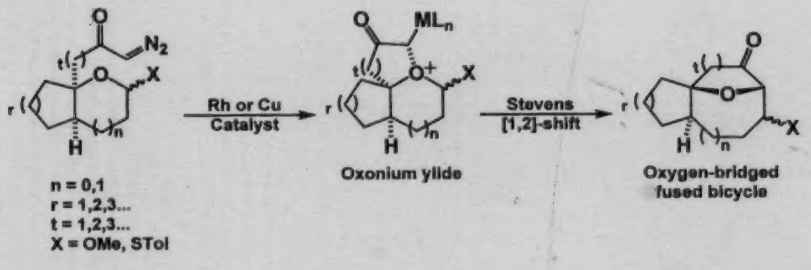
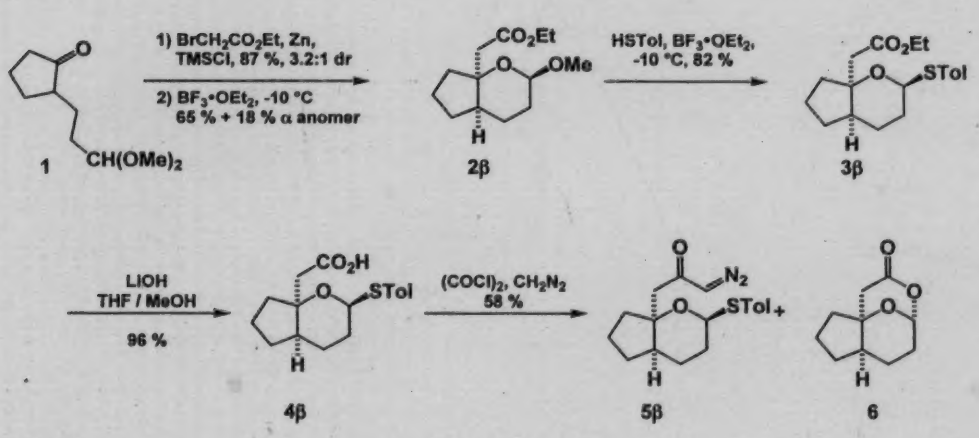


Figure 2.3: Possible variations in the synthesis of oxygen-bridged, fused carbocycles by the heteroatom-stabilized Stevens [1,2]-shift.

2.3. Results and Discussion

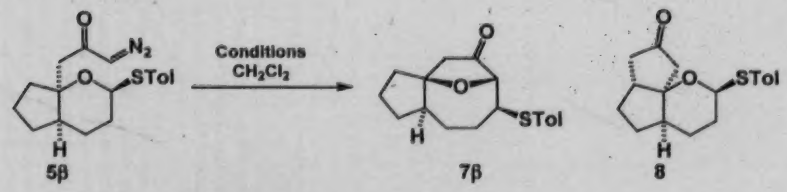
2.3.1. The initial investigation.

Dr. F.P. Marmsäter began this project, developing the methodologies necessary to demonstrate its efficacy in the synthesis of an oxygen-bridged fused 5-8 bicycle (Scheme 2.1).[20] The required diazoketone precursor was prepared from known[21] cyclopentanone **1** in 5 steps. Reformatsky addition of ethyl bromoacetate to acetal **1** afforded a 3.2:1 mixture of diastereomers, which, upon treatment with $BF_3 \cdot OEt_2$, gave the desired *cis*-fused mixed acetal **2β** in 83% yield as a mixture of anomers. This was converted to the mixed-thioacetal **3β** when stirred with HSTol and $BF_3 \cdot OEt_2$ at low temperature. Saponification of the ethyl ester with LiOH gave the carboxylic acid **4β** in quantitative yield. This was then converted into diazoketone **5β** by diazoacylation of the in situ-generated acid chloride. This step was typical of diazoacylation processes in that careful monitoring of both time and temperature were necessary to achieve good yield and chemoselectivity. Furthermore, the equivalent of acid generated in the acid chloride formation was found to degrade the mixed thioacetal, affording the corresponding acyl lactone **6**.



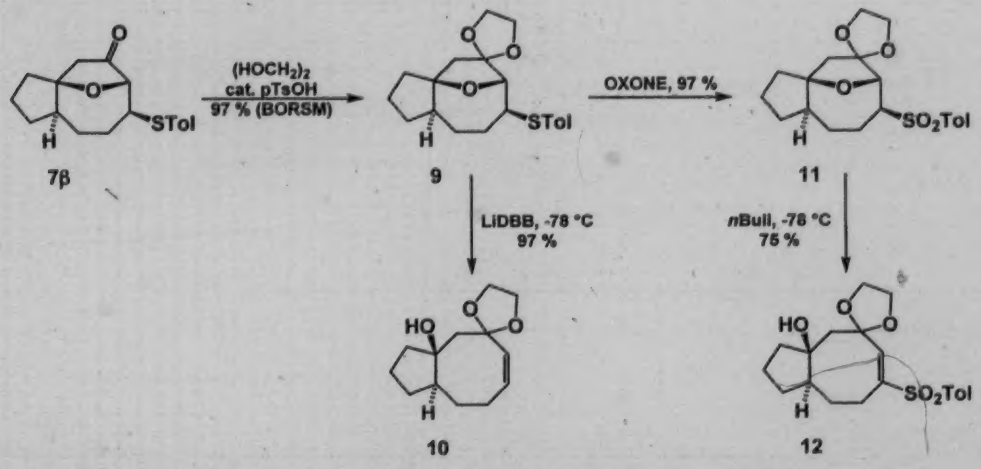
Scheme 2.1: Preparation of the Stevens rearrangement precursor.

Various rhodium and copper catalysts known to effect oxonium ylide formation were tested for their efficacy in promoting the sulfur-stabilized Stevens [1,2]-shift of diazoketone **5β** (Scheme 2.2).[22-25] Catalysts rhodium acetate, $Rh_2(OAc)_4$, and rhodium triphenylacetate[26-28] ($Rh_2(TPA)_4$) afforded the desired oxygen-bridged fused bicycle **7β** in low yield, along with greater amounts of **8**, tentatively assigned as the C-H insertion product. Treatment with $Cu(tfacac)_2$ afforded but trace amounts of both of these products, even though this was the best catalyst for the generation and rearrangement of allyl substituted oxonium ylides.[23,24,29] Upon treatment with $Cu(hfacac)_2$, **7β** was isolated in 80 % yield as a 11:1 mixture of isomers, to the exclusion of **8**. The relative stereochemistry of the product was determined by X-ray crystallography, and it was found that the [1,2]-shift occurred with near complete retention of configuration.



Scheme 2.2: The Stevens [1,2]-shift of a sulfur-stabilized anomeric carbon.

Bicycle **7β** was then converted to dioxolane **9** upon treatment with *p*-toluene-sulfonic acid and ethylene glycol, so that the ketone functionality would be protected when attempting to effect a sulfur-promoted cleavage of the bridging ether (Scheme 2.3). Treatment of **9** directly with an excess of lithium di-*tert*-butyl biphenylide (LiDBB) afforded alcohol **10** in 97 % yield. The sulfide of dioxane **9** could also oxidized with OXONE to give sulfone **11** which, upon treatment with *n*BuLi at -78 °C, also underwent cleavage of the ether to give vinyl sulfone **12** in 75 % yield.



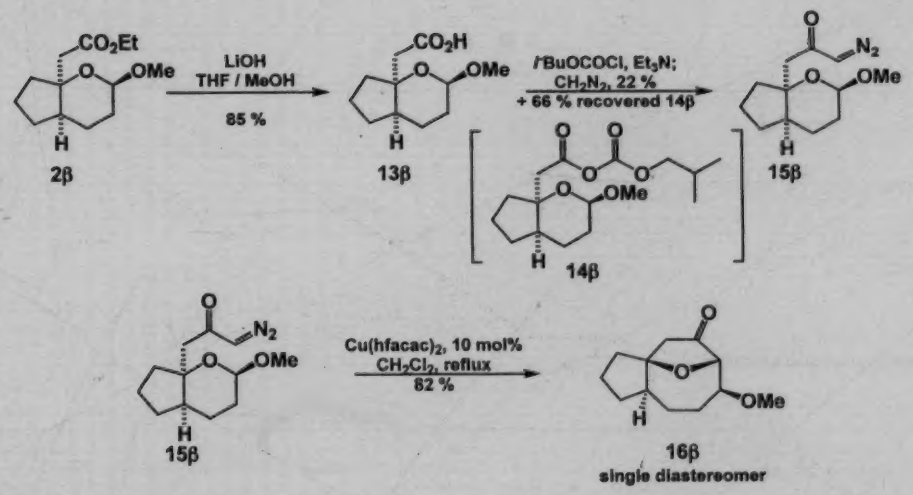
Scheme 2.3: Sulfur mediated cleavage of the bridging ether in the 5-8 bicycle.

This initial investigation showed that the original goals of the project could be attained; that a mixed, 6-membered thioacetal *cis*-fused with a 5-membered ring and that

had a pendant diazoketone side chain underwent the Stevens [1,2]-shift upon treatment with $Cu(hfacac)_2$. The product was isolated in high yield, and X-ray analysis showed that the migration occurred with near complete retention of configuration of the migrating centre. Furthermore, the remote sulfide functionality served as an anionic trigger for eliminative opening of the ether by both reductive and base-mediated protocols.

2.3.2. The oxygen-stabilized [1,2]-shift in the synthesis of a fused 5-8 bicycle.

As in the initial investigation, diazoketone **15β** was prepared by a similar method to the synthesis of **5** (Scheme 2.4). Saponification of ester **2β** with lithium hydroxide afforded carboxylic acid **13β** in 85 % yield. Given the difficulty with which the diazoketone **5β** was prepared, an alternative approach was employed in the synthesis of **15β**. Carboxylic acid **13β** was treated with *i*-butyl chloroformate to generate the mixed carbonic anhydride **14β** in quantitative yield. Treatment of this with an ethereal solution of diazomethane afforded the desired diazoketone **15β** in 22% yield, with 66 % of recovered **14β**. This low yield of the diazoketone is partially a result of the fact that the reactive acyl carbon of the mixed anhydride is less electrophilic (as can be seen from the relative ^{13}C NMR peak position)[30] and therefore is less likely to undergo diazoacylation. Upon treatment of **15β** under the carbene-transfer conditions developed for **5**, the desired oxygen-bridged 5-8 bicycle **16β** was isolated as a single diastereomer in 82 % yield.



Scheme 2.4: The Stevens [1,2]-shift of an oxygen-stabilized anomeric carbon.

2.3.3. The Mechanism of the Stevens [1,2]-shift.

The excellent levels of chemo- and diastereoselectivity observed for the Stevens [1,2]-shift of both **5β** and **15β** is worth mentioning. It was shown in Chapter 1 that 5-membered ylide formation is a favored process, and that ylide formation was particularly favored when using the electrophilic copper catalysts. The high levels of diastereoselectivity are directly related to the mechanism of the [1,2]-shift (Figure 2.4).[31] Ylide formation occurs by attack of metallocarbene **17** from the α- lone pair of electrons to make a *cis,cis* angularly-fused tricyclic oxonium ylide **18**. The [1,2]-shift probably occurs via a homolysis / recombination mechanism involving a biradical intermediate. Of the two options available for C-O bond homolysis, towards the 3° bridgehead or the heteroatom-substituted carbon, homolysis occurs to give the heteroatom-substituted radical **20**. The cationic oxygen radical is represented as the carbon-centered radical **20**, as this resonance form is stabilized by the captodative effect.[32-34] For migration to occur with retention of configuration, radical recombination must occur faster than the rate of bond rotation. This is apparently the case, given the good diastereoselectivities observed with the rearrangements. (This assumes that the catalyst is passive in the rearrangement

process, and does not contribute to the diastereoselectivity. Because the extent of catalyst involvement in the rearrangement step is not known, the mechanism is drawn without the catalyst for sake of simplicity).

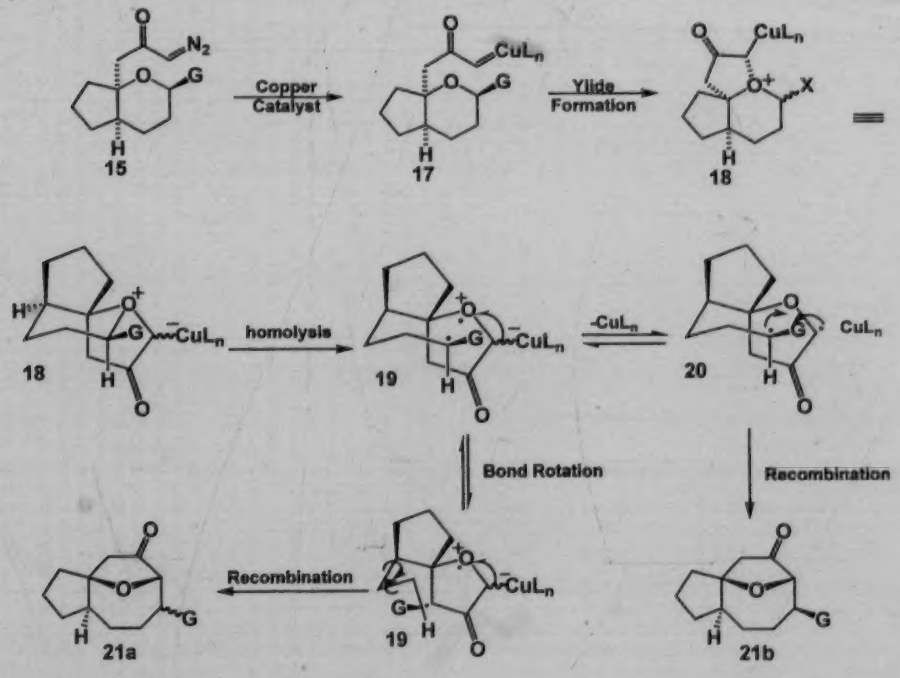
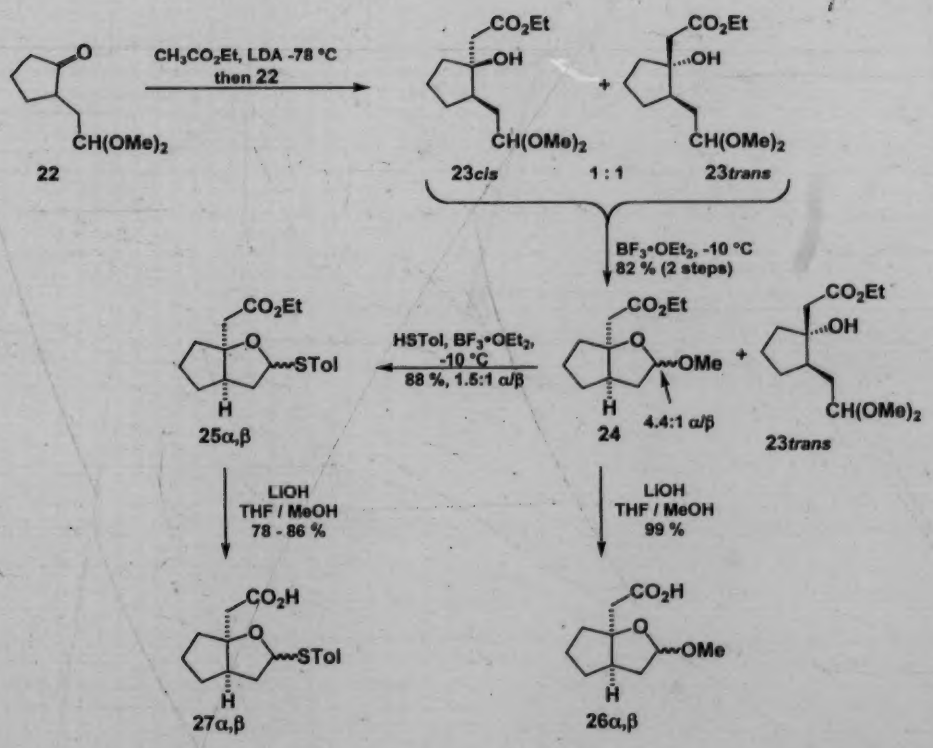


Figure 2.4: The mechanism of the [1,2]-shift, with emphasis on diastereo-selectivity.

2.3.4. Toward the synthesis of the fused 5-5 diazoketones.

Given the large number of natural products having fused, medium-sized rings, this methodology was extended to generation of oxygen-bridged 5-7 bicycles. The methods employed were analogous to the generation of the 5-8 substrates, starting from dimethyl acetal **22** (Scheme 2.5). Given the difficulty encountered in preparing the diazoketone **5** by diazoacylation, another method needed to be developed so as to promote acylation while minimizing the occurrence of side products. Cleavage of the bridging ether was also to be conducted, and the effect of the smaller 7-membered ring was to be determined.

The lithium enolate of ethyl acetate was added into the known[35,36] acetal **22** to give an equal mixture of diastereomeric alcohols **23*cis*** and **23*trans*** (Scheme 2.5). It was hoped that the diastereomeric ratio would be higher than that observed for the Reformatsky addition into **1** (3.2:1), as there was possibly a greater steric influence of a shorter acetal tether, whose branching is closer to the point of attachment on the ring. This was not observed either under Reformatsky addition of ethyl bromoacetate or the enolate of ethyl acetate, both methods giving the alcohol as an equal diastereomeric mixture. The inseparable mixture was treated directly with a full equivalent of $BF_3 \cdot OEt_2$, which gave the mixed acetal **24** as a 4.4:1 anomeric mixture in 81 % yield over the two steps. The *trans* adduct remained unchanged, and was recovered from the product mixture. Treatment of anomers **24** with *p*-TolSH in the presence of $BF_3 \cdot OEt_2$ gave mixed thioacetals **25** as a 1.5:1 α/β mixture of anomers in 88 % yield. Contrary to **3**, which was a single β-anomer, the major anomer of **25** was the α-anomer, with the thioaryl group on the convex face of the fused 5-5 ring system. Saponification of mixed acetals **24α,β** and **25α,β** occurred upon treatment with lithium hydroxide to give acids **26α,β** and **27α,β** in good to quantitative yield.

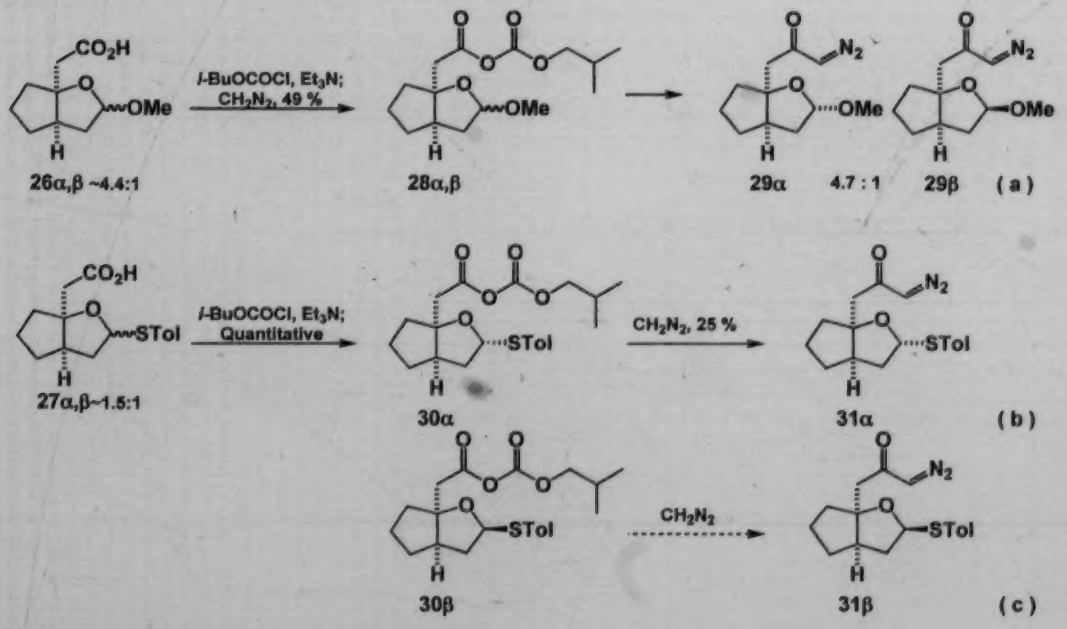


Scheme 2.5: Synthesis of the mixed acetal and mixed thioacetal diazoketone precursors.

2.3.5. Developing a new protocol for diazoacylation

It was hoped that the protocol for diazoketone formation via the isolable mixed carbonic anhydride could be optimized, as the unwanted acidic by-products are removed upon purification. Carboxylic acid **26α,β** was converted into mixed anhydride **28α,β**, and this was treated with diazomethane to afford a separable 4.7:1 mixture of diazoketones **29α** and **29β** in 49 % yield over two steps (Scheme 2.6, eq. a). Carboxylic acid **27α,β** was converted into the separable mixed carbonic anhydrides **30α** and **30β**(Scheme 2.6, eq. b). Anhydride **30α** underwent diazoacylation to give diazoketone **31α** in 25 % yield. The same attempt using the β-anhydride of **30** resulted in recovery of the anhydride as the α-anomer, with no diazoketone **31β**. Because the anomeric ratio is conserved through diazoketone formation on **29α,β**, the mixed thioacetals of **30,β** are

likely more labile than the mixed acetals of **29α,β**, as they were prone to decomposition or epimerization upon attempted diazoacylation.

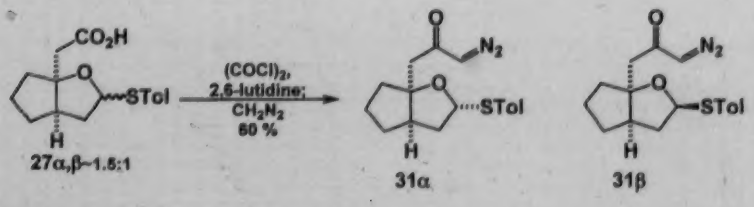


Scheme 2.6: Synthesis of the mixed acetal and mixed thioacetal diazoketones.

To determine if there were any acidic compounds present during diazoacylation that caused the degradation of the anhydride, two parallel acylation reactions were conducted, one with an equivalent of 2,6-lutidine and one without. In both cases, the diazoketone **31α** was isolated in poor yield. Because the addition of base resulted in no difference in the product distribution for these two trials, it was likely that there were no acidic by-products hampering the process. It appeared that this was simply an ineffective method for diazoacylation, and that optimization would be difficult, so we decided the original acylation procedure should be re-developed.

Several variations on the original method were attempted when re-designing the diazoacylation protocol. It was assumed that the equivalent of acid generated during the in situ acid chloride formation was responsible for the observation of acyl lactone **5**.

Attempts were made to make diazoketone **31α** using the existing protocols from **27α**, but the products were isolated in low yield, from a mixture of many components. We believed that by removing the acidic by-products of the acid chloride formation, the diazoacylation might be more productive, and proceed as desired. In analogy to that attempted with the mixed anhydride, a trial was conducted where one equivalent of 2,6-lutidine was added during acid chloride formation, but again the diazoketone was recovered in poor yield, as a mixture of isomers. We inferred that the 2,6-lutidine salts formed might still be acidic enough to isomerize the mixed thioacetal. In a subsequent attempt, the reaction was stopped after consumption of the starting acid, and the contents of the reaction flask were concentrated to give an oily mixture of crystals. This was re-dissolved in ether, the salts were removed by filtration and the filtrate re-concentrated. The oil was added to an ethereal solution of diazomethane and from this diazoketone **31α** was isolated as a single diastereomer in 50 % yield. Future trials employing this novel protocol afforded the diazoketones **31αβ** in 60 % yield (Scheme 2.7). This yield was sufficient for material throughput, and to enable trials on the Stevens [1,2]-shift.



Scheme 2.7: Synthesis of the diazoketone precursors for the synthesis of fused 5-7 bicycles.

2.3.6. The synthesis of the fused 5-7 bicycles: Determining the structure of the products.

Diazoketone **31α** was treated with two rhodium and copper catalysts to test their chemoselectivity, which was determined by G.C. analysis. For all four catalysts tested, $Rh_2(OAc)_4$, $Rh_2(tpa)_4$, $Cu(tfacac)_2$ and $Cu(hfacac)_2$, the same four product peaks were

observed by G.C. analysis of the crude reaction mixtures (Figure 2.5, Peaks 1-4). It was originally assumed that the process was lacking in chemoselectivity, affording a mixture of numerous products. The product mixtures of these trials were combined and purified, isolating the two main product mixtures seen by T.L.C.. Analysis of these product mixtures by G.C. showed that both consisted of only two compounds, accounting for the four original G.C. peaks (Figure 5, Peaks 1,3 and 2,4).

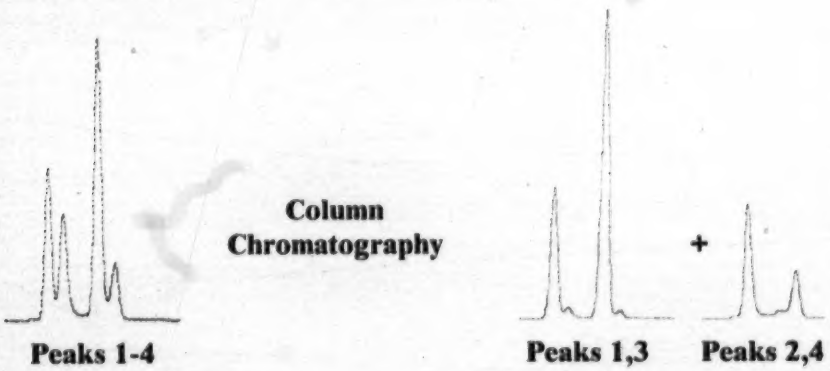
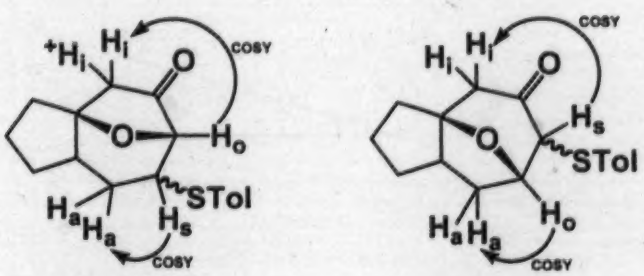


Figure 2.5: G.C. analysis of the reaction mixtures from the transition metal-catalyzed decomposition of **32α** (Peaks 1-4). Analysis of the product mixtures after column chromatography (Peaks 1,3 and 2,4).

NMR analysis of each product mixture indicated that both sets of compounds appeared consistent with the desired [1,2]-shift product **32α,β**. Based on these spectral data, we believed the [1,2]-shift had occurred with poor retention of configuration (accounting for the mixtures of would-be diastereomers seen by G.C. analysis), as did a second rearrangement, giving a mixture of products spectroscopically similar to the first (though only one diastereomer was observed by NMR analysis).

Analysis of the ^{1}H , ^{13}C, COSY and HMQC NMR data, along with the IR spectral data allowed for the determination of both structures. Analysis of the "Peaks 1,3" isomeric mixture was consistent with the desired product **32α,β** (Figure 2.6). Protons H_o and H_s were determined through the HMQC spectrum. Proton H_o was the furthest downfield aliphatic proton, and this was found to couple with the isolated protons H_i.

The next furthest downfield was proton H_s, and this was found to couple with the alkyl chain protons H_a. The carbonyl signals observed for the mixture were at 213 and 216 ppm in the ^{13}C NMR spectrum, consistent with a cyclopentanone substructure.[30] This was confirmed by the observation of the carbonyl peak in the IR spectrum at 1760 cm^{-1}. These were some of the key factors that led us to conclude the "Peaks 1,3" mixture was a diastereomeric mixture of the desired [1,2]-shift product **32α,β**.



32α,β
Peaks 1 & 3

33α,β
Peaks 2 & 4

Figure 2.6: Structures of the products from the Stevens [1,2]-shift of 31α.

Analysis of the "Peaks 2,4" isomeric mixture appeared consistent with the desired product, initially, until closer inspection. Even though this mixture appeared to consist of two isomers (based on the two peaks visible in the G.C. chromatograph), only one compound was observed upon NMR analysis. First, protons H_o and H_s were located in a manner similar to that described above. Again, H_o was the furthest downfield aliphatic proton, but in this instance, it was found to couple with protons H_a, not protons H_i (Figure 2.6). Likewise, proton H_s was found to couple with the isolated protons H_i, not protons H_a. It appeared as though the connectivity of the atoms sulfur and oxygen had reversed positions in the product. The carbonyl signal observed for the mixture was at 203 ppm in the ^{13}C NMR spectrum, consistent with this being found in a 6-membered ring, or larger.[30] This was confirmed by the observation of the carbonyl peak at 1711 cm^{-1} in the IR spectrum. These were some of the key factors that led us to conclude the "Peaks 2,4" mixture was a diastereomeric mixture of products **33α,β**.

In the proposed structure of **33α,β**, the metallocarbene carbon is bonded to the STol group, which should only be possible through the formation of a sulfonium ylide. It would be expected that 5-membered oxonium ylide formation would be the dominant process. For the alternative ylide formation to occur, either there is reversible ylide formation[13,29,37] to provide the more stable sulfonium ylide,[38] or the geometry of the bicyclic system allows for formation of the sulfonium ylide. A simple MM2 energy minimization of the metallocarbene structure showed the sulfur and oxygen to be in close proximity to the metallocarbene (Figure 2.7). Based on this, it appears that formation of either ylide should be facile. Upon formation of a 7-membered sulfonium ylide, this could undergo homolysis and subsequent [1,2]-shift to give **33α,β** (Figure 2.8).

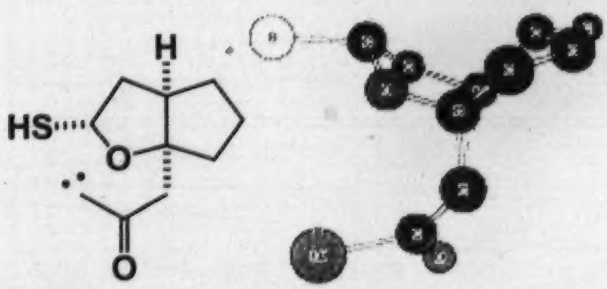


Figure 2.7: MM2 minimized 3D representation of the intermediate carbene of the α-anomer.

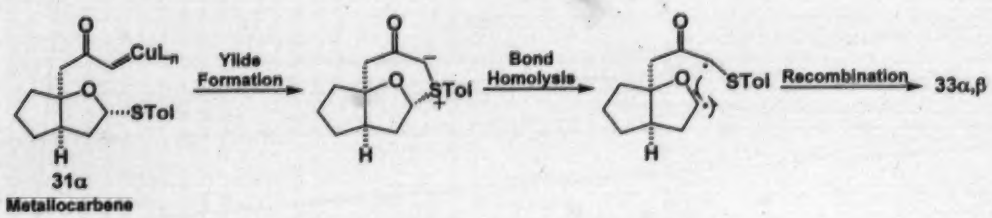
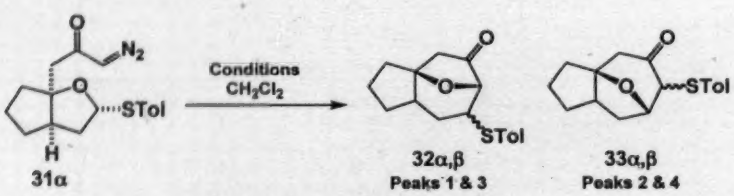


Figure 2.8: The proposed mechanism for the formation of **33α,β**.

Analysis of the G.C. chromatographs from the catalyst survey showed that the $Cu(hfacac)_2$ catalyst was the most effective at promoting the desired Stevens [1,2]-shift, affording product **32α,β** in 4.2:1 ratio over **33α,β** (Figure 2.9). The opposite was true

for Cu(tfacac)$_2$, which afforded **33α,β** over the desired product in 3:1 ratio. Both of the rhodium catalysts lacked selectivity, affording nearly equal mixtures of both products. As was seen in the [1,2]-shift for the diazoketone **5β**, the catalyst Cu(hfacac)$_2$ is the most effective at promoting the desired rearrangement.

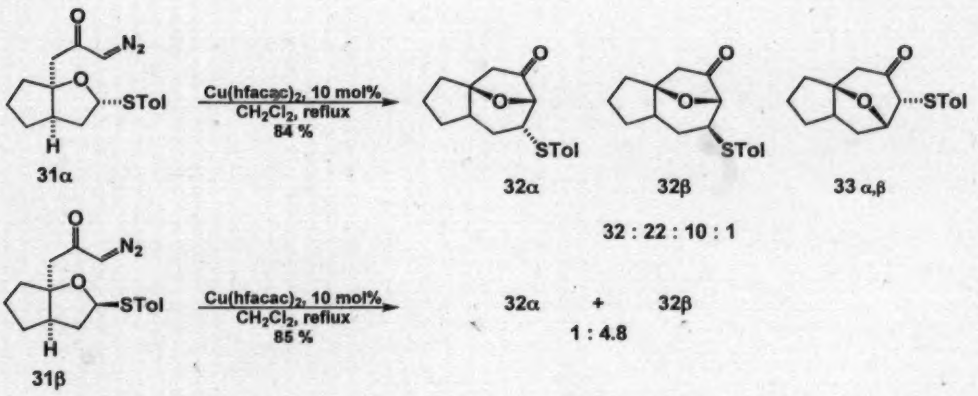


$Rh_2(OAc)_4$, 3 mol%, r.t.	1	:	1.3
$Rh_2(tpa)_4$, 3 mol%, r.t.	1	:	1
Cu(tfacac)$_2$, 10 mol%, reflux	1	:	3
Cu(hfacac)$_2$, 10 mol%, reflux	4.2	:	1

Figure 2.9: Relative area % for the products observed from the catalyst survey in the [1,2]-shift of **31α**.

2.3.7. The oxygen and sulfur-stabilized Stevens [1,2]-shift.

The [1,2]-shift on diazoketone **31α** was conducted again in the presence of Cu(hfacac)$_2$, and afforded a mixture of the desired diastereomers **32α,β**, and the side products **33α,β** (9:1 dr) in a 32 : 22 : 10 : 1 ratio in 84 % yield (Scheme 2.8). Based on the precedent of migration occurring with retention of configuration, the major diastereomer was assigned as the α-isomer. Subsequent to this, diazoketone **31β** was treated under these reaction conditions, and afforded only the desired products **32α,β** as a 1 : 4.8 ratio, in 85 % yield. The opposite selectivity observed between the substrates was anticipated as **31α** and **31β** were expected to migrate predominantly with retention of configuration. Not observed in the case of **31β** were any of the sulfonium ylide-derived products **32α,β**.



Scheme 2.8: The Stevens [1,2]-shift of a sulfur-stabilized anomeric carbon.

The lack of this second product is presumably the result of the anomeric configuration of the starting diazoketones. With none of the **33α,β** mixture being isolated (or observed by G.C. analysis of the crude reaction mixture), sulfonium ylide formation did not occur for **31β**. With the pendant diazoketone and STol groups being on opposite sides of the fused bicyclic system, it is unlikely that they would come into bonding proximity. An MM2 energy-minimized representation of the metallocarbene showed the sulfur and oxygen to be on opposite sides of the bicyclic system (Figure 2.10). Based on this, formation of the sulfonium ylides should not be possible.

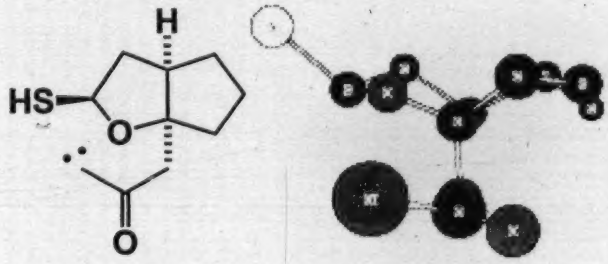
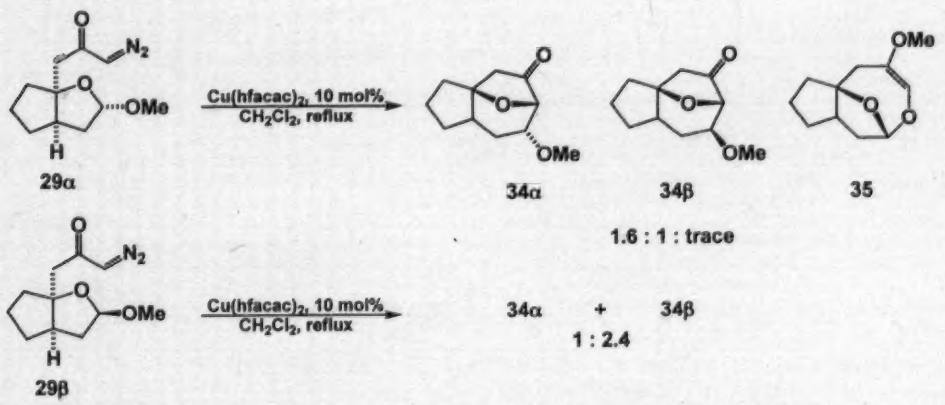


Figure 2.10: MM2 minimized 3D representation of the intermediate carbene of the β-anomer.

Diazoketones **29α** and **29β** were also treated with the standard carbene transfer conditions, and the products observed were consistent with the observations and proposals from the rearrangement of **31α,β** (Scheme 2.9). The β-isomer gave a mixture of the expected [1,2]-shift products **34α,β** as a 2.4:1 ratio of isomers (favoring **β**) in 67 % yield. The α-anomer of **29** gave a mixture of the desired products in a 1.6:1 ratio (favoring **α**), as well as a trace of **35**, in 61 % yield. Product **35** is tentatively assigned as a methyl vinyl ether, which would have resulted from 7-membered oxonium ylide formation, with subsequent [1,4]-shift of the methyl group. The ^{1}H NMR data was consistent with this, showing one vinyl and one acetal proton, and ^{13}C NMR data that showed peaks for an acetal carbon, as well as a methyl ether, with no carbonyls. As was seen previously, the β-isomer afforded solely the desired products whereas rearrangement of the α-isomer suffered from competing alternative ylide formation and subsequent rearrangement pathways.

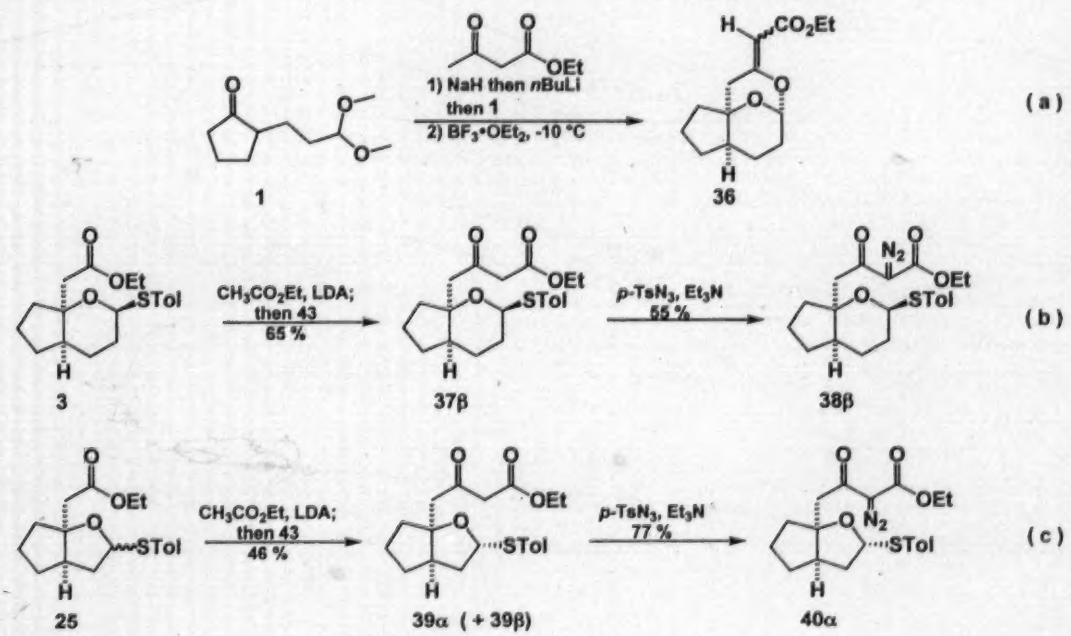


Scheme 2.9: The Stevens [1,2]-shift of an oxygen-stabilized anomeric carbon.

2.3.8. The synthesis and rearrangement of β-keto ester substrates.

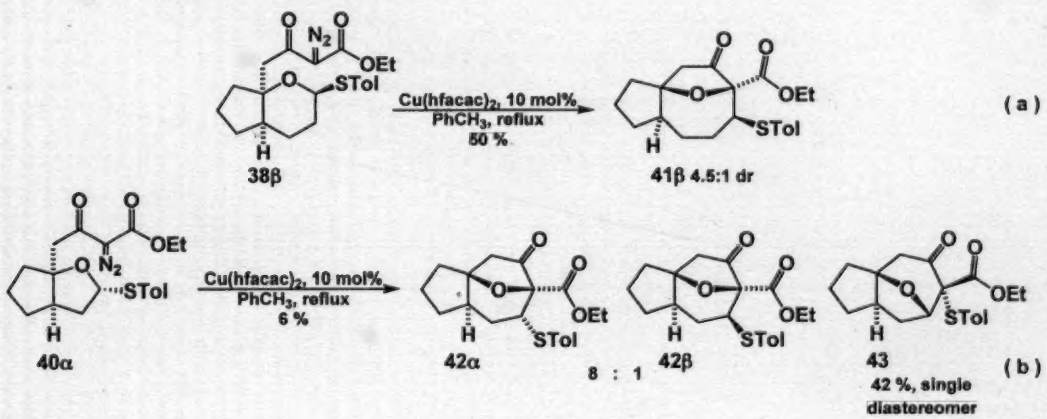
The major isomer of the oxonium ylide [1,2]-shift products in each of the six cases (both 5-7 and 5-8 ring systems) results from migration with retention, suggesting that recombination is faster than bond rotation. In either case, radical recombination must

occur with a slight molecular re-organization of the rigid, bicyclic biradical. It was observed that the degree of retention of configuration was much greater for the 8-membered case. To determine the effect of additional stabilization at the ylide centre on the selectivity of the [1,2]-shift process, two additional substrates were prepared. We initially attempted to make keto ester **37** by an aldol reaction of **1** with the dianion of ethyl acetoacetate,[39] and then carrying through the remaining sequence. The aldol process was moderately effective, but the products were prone to cyclize to the undesired product **36** in the subsequent Lewis acid-mediated transformation (Scheme 2.10, eq. a). The keto esters were subsequently prepared by intercepting previously prepared intermediates **3** and **25** (Scheme 2.10, eq. b, c). A crossed Claisen reaction between substrates **3** or **25** and the enolate of ethyl acetate gave the keto esters **37β** and **39α,β** in moderate yields. These keto esters were exposed to the standard[40] diazotransfer conditions using *p*-toluenesulfonyl azide to afford **38β** in 77 % yield, and **40α** (from **39α**) in 55 % yield.



Scheme 2.10: Synthesis of the di-stabilized α-diazo-β-keto ester substrates.

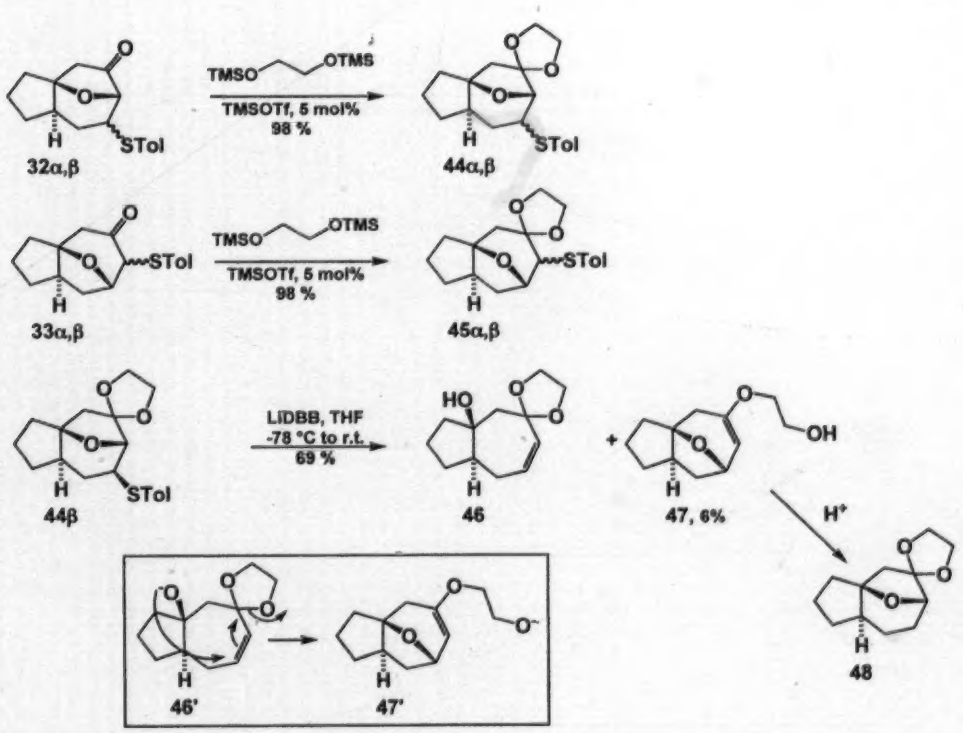
Substrate **38β** afforded the [1,2]-shift product **41** as a 4.5 : 1 ratio in 50 % yield after heating in toluene at reflux for 14 hours in the presence of $Cu(hfacac)_2$ (Scheme 2.11). Treatment of **40α** under the same conditions afforded 6 % of the [1,2]-shift products **42α** and **42β** as an 8:1 ratio, as well as 42 % of the sulfonium ylide rearrangement product **43**. The yields and reaction times are quite different from those of the mono-stabilized cases. Upon carbene transfer on **5β** and **31α**, the [1,2]-shift products were isolated in ~80 % yield, much higher than in the current investigation. Furthermore, because di-stabilized diazoketones are less prone to diazo decomposition, these last reactions required elevated temperatures and prolonged reaction times for carbene transfer to occur.[40] On the other hand, the diastereoselectivities were comparable to those observed for the mono-stabilized cases, suggesting that radical recombination is still a fast process, even with the increasingly stabilized radicals. It was interesting to isolate the sulfonium ylide product **43** as the major product from the rearrangement of **40α**. This indicates that the metallocarbene made the more stable sulfonium ylide preferentially, and rearranged to give **43** as a single diastereomer.



Scheme 2.11: The Stevens [1,2]-shift of a sulfur-stabilized anomeric carbon from a di-stabilized oxonium ylide.

2.3.9. Cleavage of the bridging ether.

The preliminary investigation by Dr. Marmsäter showed that the bridging ether could be cleaved in excellent yield by LiDBB-mediated reductive desulfurization.[20,41,42] This protocol was also employed for the reductive cleavage of the bridging ether in the 7-membered series. The ketals **44α,β** and **45α,β** were prepared in quantitative yield by treatment with bis(trimethylsiloxy)ethane with a catalytic amount of TMSOTf (Scheme 2.12). Ketal **44β** was subjected to excess LiDBB at -78 °C, which afforded the desired alcohol **46** in 69 % yield, along with 6 % of an interesting enol ether side product (**47**). This product was short-lived, and re-ketalized to **48** upon standing in $CDCl_3$, presumably due to trace amounts of acid. We believed **47** was a product of a transannular S_N2' of the alkoxide intermediate on the unsaturated ketal.[43] As further evidence, subjection of purified **46** to the reaction conditions (or *n*BuLi) afforded a mixture of **46** and **47**. It is likely that conformational preferences in the 5-7 bicycle enabled this additional reactivity, which was not observed for the 5-8 system.



Scheme 2.12: Scheme 12: Sulfur mediated cleavage of the bridging ether in the 5-7 bicycle.

2.4. Conclusions and Future Work

The methodology described herein permits the construction of fused, oxygen-bridged bicycles in relatively few steps from readily available starting materials. It was shown that heteroatom stabilization is sufficient to promote the exocyclic [1,2]-shift of mixed acetal- and thioacetal- derived oxonium ylides. The Stevens [1,2]-shift occurred in good yield with excellent diastereoselectivity for generation of the fused 5-8 bicycles. In the case of the 5-7 bicycles, the rearrangement occurred in moderate to good yield, with decreased diastereoselectivity. This is believed to be due to the increased steric congestion in the bicyclic biradical, arising from the shorter length of the heteroatom-stabilized tether. This methodology permits the stereoselective synthesis of carbocycles

with remote oxygen or sulfur functionalization on the medium sized ring. We showed that the sulfur functionality could be used to trigger the reductive cleavage of the bridging ether in excellent yield. The bicyclic carbocycle with bridgehead alcohol resulting from this cleavage is consistent with the structures of many important natural products. For the 5-7 bicycle, a side product resulting from a transannular S_N2' attack of an alkoxide on the unsaturated ketal was observed.

The 5-7 and 5-8 ring systems were efficiently prepared by this methodology. There are numerous other possibilities that can be investigated. We are currently investigating the synthesis of the 6-7 and 6-8 bicycles, employing the current methodology. We also intend to determine the feasibility of making the heteroatom-stabilized carbon part of a ring system, of potentially any size, to create tricyclic products. Given the numerous natural products that contain the structural motifs described herein, this methodology could easily be applied in total synthesis. Efforts toward the syntheses of (+)-dactylol will be described in Chapter 4. Our group is also developing a synthesis of the phorbol esters, or analogues thereof, using this methodology, as well as the natural product (+)-laurencin.

2.5. Experimental

2.5.1. General

Reactions were conducted in oven-dried (120 °C) or flame-dried glassware under a positive nitrogen atmosphere unless otherwise stated. Transfer of anhydrous solvents or mixtures was accomplished with oven-dried syringes or cannulae. Solvents were distilled before use: dichloromethane from calcium hydride; diethyl ether and tetrahydrofuran from sodium benzophenone ketyl. Thin layer chromatography (T.L.C.) was performed on plates of silica precoated with 0.25 mm Kieselgel 60 F_{254}. Flash chromatography columns were packed with 230-400 mesh silica gel. Where given,

column dimensions include outer diameters. Radial chromatography was performed on plates of silica pre-coated with 1, 2 or 4 mm silica gel 60 PF_{254} containing gypsum.

Proton nuclear magnetic resonance spectra (^1H NMR) were recorded at 400 MHz or 500 MHz on Varian Inova 400 and 500, Mercury 400, or Unity 500 spectrometers, and the chemical shifts are reported on the δ scale (ppm) downfield from tetramethylsilane. Coupling constants (*J*) are reported in Hz. Second order splitting patterns are indicated, though interpreted as if first-order. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; dd, doublet of doublets, etc. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 125 MHz and are reported (ppm) relative to the center line of a triplet at 77.23 ppm for deuterochloroform. Infrared (IR) spectra were measured with a Nicolet Magna 750 FT-IR infrared spectrophotometer. Mass spectra were determined on a Kratos Analytical MS-50 (EI) or Applied Biosystems Mariner Biospectrometry Workstation (ESI). Elemental analyses were obtained at the University of Alberta on a Carlo Erba CHNS-O EA 1108 Elemental Analyzer.

2.5.2. Substrate Syntheses

Acid 13β. To a solution of hemiacetal **2β** (410 mg, 1.69 mmol) in THF (3.0 mL) and methanol (3.0 mL) was added a 2M solution of LiOH (1.7 mL). The reaction was stirred for 16 hours at r.t., during which time the reaction mixture turned slightly yellow. The reaction was diluted with water (15 mL) and Et_2O (15 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was washed with ether (15 mL). The aqueous layer was then acidified with 0.5M HCl to pH~3, resulting in a cloudy suspension. To this was added ethyl acetate (20 mL) and the resulting were layers separated. The aqueous layer was washed with 3 portions of ethyl acetate (20 mL) and the combined organic extracts were washed with water then brine, dried over magnesium sulfate, filtered and concentrated to yield the acid, as a yellow oil (307 mg, 85 %): IR (CH_2Cl_2 cast) 3500-2400, 2946, 2891, 2680, 1704, 1451, 1408, 1391, 1363, 1335, 1322,

1307 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.90 (br. s, 1H), 4.66-4.64 (m, 1H), 3.41 (s, 3H), 2.94 (d, J_{AB} = 14.1 Hz, 1H), 2.35 (d, J_{AB} = 14.1 Hz, 1H), 2.16 (m, 1H), 1.91 – 1.80 (m, 3H), 1.78 – 1.72 (m, 4H), 1.66 – 1.58 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 98.9, 83.8, 56.0, 41.2, 41.0, 38.9, 28.1, 26.2, 21.7, 21.5; HRMS (EI) calcd for $C_{11}H_{18}O_4$ (M^+) 214.1205, found 214.1192; Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.73. Found: C, 61.31; H, 8.47.

***(1R*,3R*,6S*)*-3-Methoxy-2-oxabicycl[4.3.0]nonane-1-acetic Acid Isobutyryl-carbonic Mixed Anhydride (14β).** To a solution of the acid (100 mg, 0.47 mmol) in Et_2O (2 mL) at 0 °C was added Et_3N (68 μL, 0.49 mmol) followed by isobutyl chloroformate (65 μL, 0.49 mmol) and the reaction was stirred for 4 hours, resulting in an off-white precipitate. The reaction mixture was filtered through a fritted filter (D), the residue was rinsed with Et_2O (20 mL) and the combined filtrates were concentrated to give 149 mg of anhydride **14β** as a yellow oil in 100 % yield, which was used directly in the next step: R_f 0.66 (30 % EtOAc / hexanes); IR (CH_2Cl_2 cast) 2956, 2874, 1819, 1735, 1457, 1392, 1369, 1336, 1307 1230, 1207 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.60 (dd, J = 8.8, 3.0 Hz, 1H), 4.04 (d, J = 6.7 Hz, 2H), 3.42 (s, 3H), 3.08 (d, J_{AB} = 13.6 Hz, 1H), 2.42 (d, J_{AB} = 13.6 Hz, 1H), 2.16 (m, 1H), 2.01 (sept, J = 6.7 Hz, 1H), 1.94 - 1.83 (m, 2H), 1.82 – 1.68 (m, 5H), 1.64 – 1.53 (m, 3H), 0.97 (d, J = 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 149.3, 98.7, 83.5, 75.7, 56.2, 41.2, 40.9, 39.7, 28.0, 27.8, 25.9, 21.9, 21.8, 19.0; HRMS (EI) calcd for $C_{16}H_{26}O_6$ (M^+) 314.1729; found 314.1721.

Diazoketone 15β. Into a solution of freshly prepared diazomethane (12 mmol) in Et_2O (40 mL) at –15 °C was added a solution of the mixed anhydride (250 mg, 0.80 mmol) in Et_2O (10 mL), and the resulting mixture was allowed to stir overnight as the cold bath expired. A stream of N_2 was applied to the system to allow for slow evaporation of both excess diazomethane and solvent, and the resulting yellow oil was diluted in ether, and passed through a short pad of silica gel in a fritted filter, eluting with ether. This was then concentrated and the resulting oil was purified by radial chromatography (2 mm plate, solvent ramp: 100 mL each of 5 %, 10 % then 15 % EtOAc / hexanes until the

product was recovered) to yield 152 mg of starting material as well as 51 mg of **15β** as a yellow oil in 22 % yield, 70 % BORSM: R_f 0.33 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 3082, 2953, 2869, 2101, 1733, 1637, 1457, 1364, 1226, 1187 cm^{-1}; ^1H NMR (500 MHz, –20 °C, $CDCl_3$) δ 5.50 (s, 1H), 4.64 (dd, J = 8.4, 3.1 Hz, 1H), 3.46 (s, 3H), 2.96 (d, J_{AB} = 13.7 Hz, 1H), 2.33 (d, J_{AB} = 13.7 Hz, 1H), 2.09 (ddd, J = 12.8, 8.2, 4.0 Hz, 1H), 1.86 (m, 2H), 1.82 – 1.66 (m, 5H), 1.66 – 1.54 (m, 3H); ^{13}C NMR (125 MHz, –60 °C, $CDCl_3$,) δ 193.0, 98.2, 83.8, 56.7, 56.6, 46.0 41.1, 39.2, 26.8, 25.2, 21.4, 21.0; HRMS (EI) calcd for $C_{12}H_{17}N_2O_3$ ($M\text{-}H^+$) 237.1239; found 237.1225.

Ethyl Acetate Adducts of 22: Into a stirring solution of diisopropylamine (3.66 mL, 26.1 mmol) in THF (30 mL) at –78 °C was added *n*BuLi (10.9 mL of 2.4M solution, 26.1 mmol) and the resulting mixture was stirred at –78 °C for 30 minutes. This was then warmed to 0 °C over several minutes and stirred for another 30 minutes before being cooled once again to –78 °C. Ethyl acetate (2.44 mL, 25 mmol) was added dropwise, and the mixture was stirred for 1 hour. A solution of 2-[(2,2-dimethoxy)ethyl]cyclopentanone **22**[35, 36] (4.0 g, 23 mmol) in THF (10 mL) was added dropwise to the above mixture and the reaction mixture was stirred at –78 °C until the reaction was complete by T.L.C. analysis (4 h). The reaction mixture was quenched with saturated ammonium chloride (25 mL). After separation of the phases, the aqueous layer was extracted with Et_2O (3 x 15 mL) and the combined organic extracts were washed with water (50 mL) and brine (50 mL), dried (magnesium sulfate), filtered and concentrated to afford 5.64 g of the crude product in 95.3 % yield as a 1.7:1 mixture of inseparable **23*cis*** and **23*trans*** isomers (ratio determined by ^1H NMR integration of methoxy singlets), which was carried on without further purification.

***Cis* isomer**: R_f 0.23 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 3513, 2953, 2830, 1731, 1447, 1371, 1334, 1190, 1125, 1057, 964 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.37 (dd, J = 7.8, 3.5 Hz, 1H), 4.14 (q, J = 7.0 Hz, 2H) 3.28 (s, 6H), 3.23 (br.s, 1H), 2.66 (d, J_{AB} = 15.5 Hz, 1H), 2.33 (d, J_{AB} = 15.5 Hz, 1H), 1.88 – 1.65 (m, 5H), 1.60 – 1.50 (m, 4H), 1.25 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.7, 103.3, 53.4, 52.8, 45.7, 37.9, 32.7, 30.4, 21.0; LRMS (ESI) calcd for $C_{13}H_{24}O_5Na$ (M^+) 283.1; found 283.1; Anal.

Calcd for $C_{13}H_{24}O_5$: C, 59.98; H, 9.29. Found: C, 59.58; H, 10.01. (Data obtained from the inseparable mixture of diastereomers)

Trans* isomer**: R_f 0.23 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 3511, 2953, 2830, 1724, 1447, 1371, 1332, 1199, 1124, 1058, 966 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.42 (dd, J = 7.1, 4.4 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H) 3.81 (br s, 1H) 3.30 and 3.26 (2s, 6H), 2.47 (d, J_{AB} = 15.6 Hz, 1H), 2.38 (d, J_{AB} = 15.6 Hz, 1H), 2.03 – 1.94 (m, 2H), 1.82 – 1.76 (ddd, J = 13.9, 7.1, 4.2 Hz, 1H), 1.75 – 1.65 (m, 3H), 1.61 – 1.51 (m, 2H), 1.29 – 1.20 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 103.8, 80.7, 61.0, 53.5, 52.2, 45.6, 39.7, 38.4, 33.2, 29.3, 20.8, 14.4; LRMS (ESI) calcd for $C_{13}H_{24}O_5Na$ (M^+) 283.1; found 283.1; Anal. Calcd for $C_{13}H_{24}O_5$: C, 59.98; H, 9.29. Found: C, 59.85; H, 9.29. (Data obtained from a pure sample of the **23trans* isomer recovered after the formation of **24** from the inseparable mixture of *cis*- and *trans*-isomers.)

Mixed Acetals 24α,β. To a solution of the **23***cis* and **23***trans* ethyl acetate adducts (11.2 g, 43.3 mmol) in CH_2Cl_2 (1.0 L) at –15 °C (acetone / ice bath) was added BF_3•OEt_2 (5.50 mL, 43.3 mmol) and the reaction was stirred for 20 minutes, at which time T.L.C. showed consumption of the *cis* isomer and a mixture of **24α,β**, together with the unreacted **23***trans* isomer. The reaction was quenched with Et_3N (6 mL) and water (500 mL) and the resulting phases were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with water and brine, then dried (magnesium sulfate), filtered and concentrated. The crude product was purified by column chromatography (silica gel; EtOAc / hexanes 3:7) to afford recovered **23***trans* adduct and 3.85 g of **24α,β** as a 4.4:1 mixture of α and β anomers in 62 % yield as a yellow oil (ratio based on integration of OMe singlets): R_f 0.53 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2950, 2868, 2829, 1735, 1467, 1447, 1369, 1342, 1300, 1208, 1103, 1049 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.97 (d, J = 5.2 Hz, 0.8H) overlapping with 4.96 (m, 0.2H) 4.11 (q, J = 7.1 Hz, 2H), 3.30 (s, 2.4H), 3.28 (s, 0.6H), 2.85 (d, J_{AB} = 14.4 Hz, 0.8H), 2.67 – 2.61 (m, 0.8H), 2.64 (d, J_{AB} = 14.4 Hz, 0.2H), 2.63 (d, J_{AB} = 14.4 Hz, 0.8H), 2.56 (m, 0.2H), 2.52 (d, J_{AB} = 14.4 Hz, 0.2H), 2.27 (ddd, J = 13.3, 9.5, 5.7 Hz,

0.2H), 2.20 (dd, J = 13.3. 9.3 Hz, 0.8H) 1.96 – 1.87 (m, 1H), 1.73 – 1.56 (m, 4.8H), 1.46 – 1.41 (m, 1.2H), 1.24 (t, J = 7.2 Hz, 2.4H), 1.23 (t, J = 7.2 Hz, 0.6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ Major: 171.4, 106.7, 93.8, 60.4, 54.7, 46.2, 46.0, 41.4, 38.9, 33.6, 24.0, 14.5, Minor: 171.2, 107.0, 94.9, 60.5, 54.9, 45.4, 44.9, 40.5, 40.4, 34.2, 24.5, 14.5; HRMS (EI) calcd for $C_{12}H_{20}O_4$ (M^+) 228.1362; found 228.1359; Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 62.90; H, 9.43.

Mixed Thioacetals 25α,β. To a solution of **24α,β** (50 mg, 0.22 mmol) and *p*-thiocresol (27 mg, 0.22 mmol) in CH_2Cl_2 (22 mL) at –45 °C was added BF_3•OEt_2 (28 μL, 0.22 mmol) and the reaction was stirred until deemed complete by T.L.C.. After 2 hours only a trace of starting acetals was observed; the reaction was quenched with Et_3N (0.5 mL) and water (15 mL) and the resulting bi-layer was separated. The aqueous phase was extracted with CH_2Cl_2 (15 mL) and the combined organic extracts were washed with water (30 mL), brine (30 mL), dried with magnesium sulfate, filtered and concentrated. The crude product was first passed through a pad of silica gel in a fritted filter, eluting with Et_2O, and then purified by radial chromatography (silica gel, 2 mm plate, solvent ramp: 100 mL each of 3 %, 6 % then 9 % EtOAc / hexanes until the product was recovered) to afford the product, a yellow oil, as a 1.5 : 1 mixture of partially separable anomers (**25α** and **25β**) in 88 % yield (57 mg) based on recovered **24α,β** (4 mg).

Major Anomer 25α: R_f 0.63 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2954, 2867, 1731, 1493, 1446, 1369, 1340, 1300, 1195, 1094, 1054, 1034 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 8.2 Hz, 2H), 7.04 (d, J = 8.2 Hz, 2H), 5.51 (dd, J = 6.9, 5.4 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 2.94 (d, J_{AB} = 14.6 Hz, 1H), 2.85 (d, J_{AB} = 14.6 Hz, 1H), 2.74 (ddd, J = 8.4, 5.2, 3.2 Hz, 1H), 2.29 – 2.24 (m, 1H), 2.28 (s, 3H), 2.08 (ddd, J = 13.6, 6.8, 5.2 Hz, 1H), 1.97 – 1.92 (m, 1H), 1.84 – 1.76 (m, 1H), 1.73 – 1.58 (m, 3H), 1.49 – 1.44 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 137.2, 132.2, 131.8, 129.8, 95.0, 88.3, 60.5, 46.9, 44.8, 41.0, 39.2, 33.3, 24.5, 21.3, 14.4; HRMS (EI) calcd for $C_{18}H_{24}O_3S$ (M^+) 320.1446; found 320.1419; Anal. Calcd for $C_{18}H_{24}O_3S$: C, 67.47; H, 7.55. Found: C, 67.24; H, 7.57.

Minor Anomer 25β: R_f 0.63 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 3511, 2953, 2830, 1724, 1447, 1371, 1332, 1199, 1124, 1058, 966 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 5.25 (dd, J = 8.2, 6.4 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H) , 2.61 (s, 2H), 2.66 – 2.53 (m, 3H), 2.29 (s, 3H), 2.04 (m, 1H), 1.78 – 1.50 (m, 6H), 1.22 (t, J = 8.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 137.0, 131.7, 131.6, 129.7, 94.7, 86.2, 60.6, 46.8, 43.9, 41.0, 39.4, 33.8, 24.2, 21.3, 14.5; HRMS (EI) calcd for $C_{18}H_{24}O_3S$ (M^+) 320.1446; found 320.1428.

Diazoketones 29α,β. To a solution of mixed acetals **24α,β** (1.00 g, 4.38 mmol) in THF (8 mL) and methanol (8 mL) was added a 2.0M solution of LiOH (4.38 mL). The reaction was stirred for 16 hours at room temperature, during which time the reaction mixture turned slightly yellow. The reaction was diluted with water (20 mL) and Et_2O (20 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was washed with ether (20 mL). The aqueous layer was then acidified with 0.5M HCl to pH ~3, resulting in a cloudy suspension. This was then diluted with ethyl acetate (30 mL) and the resulting layers were separated. The aqueous layer was washed with 3 portions of ethyl acetate (20 mL) and the combined organic extracts were washed with water then brine, dried over magnesium sulfate, filtered and concentrated to give 870 mg of the acids **26α,β** as a yellow oil in 99 % yield: IR (CH_2Cl_2 cast) 3600-2500, 2949, 1708, 1468, 1440, 1409, 1339, 1300, 1218 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.8 (br s, 1H), 4.99 (d, J = 5.2 Hz, 1.0H), 3.30 (s, 2.4H), 3.28 (s, 0.6H), 2.90 (d, J_{AB} = 14.9 Hz, 0.8H), 2.64 (d, J_{AB} = 14.6 Hz, 0.2H), 2.63 (d, J_{AB} = 14.9 Hz, 0.8H), 2.56 (d, J_{AB} = 14.6 Hz, 0.2H), 2.49 (ddd, J = 4.6, 1.2 Hz, 0.2H), 2.27 (ddd, J = 13.6, 9.8, 5.7 Hz, 0.2H), 2.20 (dd, J = 13.3, 9.2 Hz, 0.8H), 1.98 – 1.80 (m, 1.6H), 1.75 – 1.55 (m, 5.2H), 1.43 (m, 1.0H); ^{13}C NMR (125 MHz, $CDCl_3$) δ Major Anomer: 176.0, 107.1, 93.5, 55.0, 46.5, 46.0, 41.1, 38.9, 33.7, 24.0; Minor Anomer: 176.0, 107.2, 94.7, 55.1, 44.8, 40.2, 40.1, 34.0, 24.6; HRMS (EI) calcd for $C_{10}H_{16}O_4$ (M^+) 200.1049; found 200.1051.

To a solution of the anomeric acids **26α,β** (800 mg, 4.0 mmol) in Et_2O (50 mL) at 0° C was added Et_3N (585 μL, 4.4 mmol) followed by isobutyl chloroformate (574 μL, 4.4 mmol) and the reaction was stirred for 2.5 hours, resulting in the formation of an off-

white precipitate. The reaction mixture was filtered through a fritted filter (D), rinsed with Et_2O (50 mL) and concentrated to give 1.09 g of the mixed anhydrides in 91 % yield as a yellow oil: R_f 0.62 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2958, 2784, 2831, 1804, 1760, 1470, 1452, 1396, 1370 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) Major **α** Anomer δ 5.00 (d, J = 5.3 Hz, 1H), 4.03 (d, J = 7.1 Hz, 2H), 3.31 (s, 3H), 3.03 (d, J_{AB} = 15.3 Hz, 1H), 2.80 (d, J_{AB} = 15.3 Hz, 1H), 2.66 (m, 1H), 2.23 (dd, J = 13.3, 9.2 Hz, 1H), 2.01 (sept, J = 6.8 Hz, 1H) 2.00 (m, 1H), 1.76 (m, 1H), 1.68 (ddd, J = 12.0, 7.5, 5.3 Hz, 1H), 1.63 (m, 3H), 1.46 (m, 1H), 0.95 (d, J = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ Major **α** Anomer: 165.8, 149.4, 106.9, 93.1, 75.7, 54.8, 46.4, 45.7, 41.3, 38.8, 33.5, 27.8, 24.0, 19.0; Minor **β** Anomer: 165.6, 149.4, 106.7, 94.4, 75.5, 54.8, 45.6, 44.6, 41.4, 38.9, 34.3, 33.6, 24.5, 19.0; HRMS (EI) calcd for $C_{15}H_{23}O_6$ ($M\text{-}H^+$) 299.1495; found 299.1499.

A solution of anomeric mixed anhydrides **28α,β** (624 mg, 2.2 mmol) in Et_2O (10 mL) was added via cannula to a solution of freshly prepared diazomethane (20 mmol) in Et_2O (60 mL) at –15 °C, and the resulting was mixture stirred for 16 hours as the cooling bath expired. A gentle stream of N_2 was applied to the system to allow for slow evaporation of both excess diazomethane and solvent, and the resulting yellow oil was diluted in ether (20 mL), passed through a short pad of silica gel in a fritted filter, eluting with copious ether. This was then concentrated and the resulting oil was purified by radial chromatography (silica gel, 4 mm plate, solvent ramp: 100 mL each of 3 %, 6 %, 9 % then 12 % EtOAc / hexanes until the products were recovered) to give 228 mg of **29α,β** as an inseparable 4.7:1 mixture of anomers in 49 % yield as a bright yellow oil, as well as a trace of starting material (not quantified): R_f 0.23 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 3087, 2949, 2868, 2829, 2102, 1817, 1735, 1637, 1440, 1361 cm^{-1}; ^1H NMR (500 MHz, –40 °C $CDCl_3$) δ 5.67 (s, 0.8H), 5.52 (s, 0.2H), 5.01 (m, J = 5.1 Hz, 1H), 3.36 (s, 2.4H), 3.30 (s, 0.6H), 2.94 (d, J_{AB} = 14.3 Hz, 0.8H), 2.69 (d, J_{AB} = 13.5 Hz, 0.2H), 2.60 (m, 1H), 2.55 (d, J_{AB} = 14.3 Hz, 0.8H), 2.47 (d, J_{AB} = 13.5 Hz, 0.2H), 2.20 (dd, J = 13.5, 9.5 Hz, 1H), 1.90 (m, 1H), 1.70 – 1.45 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, –60 °C) Major **α** Anomer: δ 194.1, 106.4, 93.4, 56.0, 54.9, 52.8, 46.4, 40.3, 38.1, 32.5, 23.4; Minor **β** Anomer: δ 194.1, 106.5, 95.4, 56.8, 54.7, 50.8, 44.2, 40.3, 39.9, 33.6, 24.2; HRMS (ESI) calcd for $C_{11}H_{16}N_2O_3Na$ (M^+) 247.1059; found 247.1060.

Diazoketones 31α,β. Preparation and characterization of individual acid anomers is given below. For convenience, they were usually prepared as a mixture of anomers and converted into the separable diazoketones.

To a solution of mixed acetal **25α** (423 mg, 1.3 mmol) in THF (5 mL) and methanol (5 mL) was added a 2.0M solution of LiOH (1.3 mL). The reaction was stirred for 16 hours at room temperature, during which time the reaction mixture turned slightly yellow. The reaction was diluted with water (20 mL) and Et_2O (20 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was washed with ether (15 mL). The aqueous layer was then acidified with 0.5M HCl to pH ~3, resulting in a cloudy suspension. This was then diluted with ethyl acetate (40 mL) and the resulting layers were separated. The aqueous layer was washed with 3 portions of ethyl acetate (20 mL) and the combined organic extracts were washed with water (50 mL) then brine (50 mL), dried over magnesium sulfate, filtered and concentrated to give 333 mg of **27α** as a yellow oil in 86 % yield: IR (CH_2Cl_2 cast) 3500-2400, 2953, 2867, 1708,1597, 1493, 1443, 1408, 1300, 1231. 1133, 1093 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, J = 8.2 Hz, 2H), 7.07 (d, J = 8.2 Hz, 2H), 5.56 (dd, J = 6.0, 6.0 Hz, 1H), 3.03 (d, J_{AB} = 14.8 Hz, 1H), 2.74 (d, J_{AB} = 14.8 Hz, 1H), 2.63 (m, 1H), 2.32 – 2.25 (m, 1H), 2.29 (s, 3H), 2.14 (ddd, J = 13.4, 6.8, 5.0 Hz, 1H), 1.98 – 1.92 (m, 1H), 1.88 – 1.79 (m, 1H), 1.70 – 1.58 (m, 3H), 1.52 – 1.46 (m, 1H), (COOH peak not measured); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.8, 137.9, 132.5, 130.8, 130.0, 94.7, 88.7, 47.5, 44.9, 40.5, 39.0, 33.0, 24.5, 21.3; HRMS (EI) calcd for $C_{16}H_{20}SO_3$ (M^+) 292.1133; found 292.1135.

Following the same procedure as above, **25β** (142 mg, 0.44 mmol) was converted into 100 mg of the corresponding acid **27β** in 78 % yield as a white solid: m.p. 115 – 116 °C; IR (CH_2Cl_2 cast) 3500 - 2500, 2949, 2865, 1707, 1493, 1439, 1411, 1299, 1232. 1146, 1093 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.4 (br s, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 5.28 (dd, J = 8.2, 5.6 Hz, 1H), 2.69 (d, J_{AB} = 14.8 Hz, 1H), 2.57 (d, J_{AB} = 14.8 Hz, 1H), 2.60 – 2.51 (m, 2H), 2.29 (s, 3H), 2.10 (m, 1H), 1.78 – 1.54 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.8, 137.7, 132.4, 130.7, 129.9, 94.4, 86.5, 47.6, 43.6,

40.6, 39.0, 33.6, 24.3, 21.3; HRMS (EI) calcd for $C_{16}H_{20}SO_3$ (M^+) 292.1133; found 292.1141; Anal. Calcd for $C_{16}H_{20}O_3S$: C, 65.72; H, 6.89. Found: C, 65.21; H, 7.07.

To a solution of both anomeric acids (**27α** + **27β**) (1.0 g, 3.42 mmol) in CH_2Cl_2 (140 mL) at –15 °C was added 2,6-lutidine (478 μL, 4.1 mmol) followed by oxalyl chloride (36 μL, 4.1 mmol) and DMF (2 drops, ~10 μL), resulting in the evolution of copious amounts of gas. The reaction was stirred for 4 hours, and solvent was removed by rotary evaporation to give a yellow oil entrained in a white precipitate. This material was redissolved in ether (50 mL) and the suspension filtered through a fritted filter (D), washing several times with ether (50 mL). The ethereal solution of the acid chloride was condensed to a lesser volume (~50 mL) and added via cannula to a solution of freshly prepared diazomethane (60 mmol) in Et_2O (200 mL) at –15 °C, and the resulting mixture was stirred for 16 hours as the cooling bath expired. A gentle stream of N_2 was applied to the system to allow for slow evaporation of both excess diazomethane and solvent, and the resulting yellow oil was diluted in ether (40 mL), passed through a short pad of silica gel in a fritted filter, eluting with copious ether. The filtrate was concentrated and the resulting oil was purified by radial chromatography (silica gel, 4 mm plate, solvent ramp: 100 mL each of 3 %, 6 %, 9 % then 12 % EtOAc / hexanes until the products were recovered) to yield **31α** (410 mg) and **31β** (240 mg), as yellow oils in a combined overall yield of 60 %.

Major Anomer 31α: R_f 0.32 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 3105, 2953, 2866, 2100, 1636, 1492, 1450, 1358, 1241, 1162, 1093, 1061, 1017 cm^{-1}; ^1H NMR (500 MHz, –60 °C, $CDCl_3$) δ 7.36 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 5.81 (dd, J = 6.2, 2.7 Hz, 1H), 5.12 (s, 1H), 3.23 (d, J_{AB} = 13.2 Hz, 1H), 2.66 (app. q, J = 7.3 Hz, 1H), 2.49 (d, J_{AB} = 13.2 Hz, 1H), 2.37 – 2.30 (m, 1H), 2.32 (s, 3H), 2.17 – 2.11 (m, 1H), 1.84 – 1.52 (m, 6H); ^{13}C NMR (125 MHz, -60°C, $CDCl_3$) δ 194.3, 136.5, 131.3, 129.8, 129.8, 95.0, 87.0, 56.2, 52.1, 47.4, 29.8, 98.0, 32.2, 23.5, 21.1; HRMS (ESI) calcd for $C_{17}H_{20}N_2O_2SNa$ (M^+) 339.1143; found 339.1147; Anal. Calcd for $C_{17}H_{20}N_2O_2S$: C, 64.53; H, 6.37; N, 8.85. Found: C, 64.92; H, 6.13; N, 8.66.

Minor Anomer 31β: R_f 0.26 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 3081, 2952, 2865, 2100, 1636, 1492, 1449, 1358, 1161, 1093, 1051, 1016 cm^{-1}; ^1H NMR (500 MHz, –60 °C, $CDCl_3$) δ 7.39 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 5.53 (s, 1H), 5.14 (dd, J = 9.7, 5.4 Hz, 1H), 2.66 (d, J_{AB} = 13.6 Hz, 1H), 2.60 (app. q, J = 7.6 Hz, 1H), 2.53 (d, J_{AB} = 13.6 Hz, 1H), 2.48 (ddd, J = 13.0, 9.0, 5.5 Hz, 1H), 2.34 (s, 3H), 2.04 – 1.98 (br m, 1H), 1.66 – 1.46 (m, 6H); ^{13}C NMR (125 MHz, –60 °C $CDCl_3$) δ 193.8, 137.5, 131.8, 129.7, 129.5, 94.0, 84.9, 56.7, 50.0, 46.8, 39.6, 38.5, 32.7, 23.4, 21.2; HRMS (ESI) calcd for $C_{17}H_{20}N_2O_2SNa$ (M^+) 339.1143; found 339.1143; Anal. Calcd for $C_{17}H_{20}N_2O_2S$: C, 64.53; H, 6.37; N, 8.85. Found: C, 64.40; H, 6.58; N, 8.52.

Ethyl Acetate Adduct 37β: Into a stirring solution of diisopropylamine (1.44 μL, 10.31 mmol) in THF (7 mL) at –78 °C was added *n*BuLi (4.37 mL of 2.36M solution, 10.31 mmol) and the resulting mixture was stirred at –78 °C for 30 minutes. This was then warmed to 0 °C over several minutes and stirred for another 30 minutes before being cooled once again to –78 °C. Ethyl acetate (968 μL, 9.9 mmol) was added dropwise, and the mixture was stirred for 1 hour. A solution of anomer **3** (662 mg, 1.98 mmol, 1 eq) in THF (1 mL) was added dropwise to the above mixture and the reaction mixture was stirred overnight, allowing the cooling bath to expire. The reaction was then diluted with ethyl ether (10 mL) and quenched by the addition of saturated ammonium chloride solution (10 mL). After separation of the phases, the aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic extracts were washed with water (15 mL) and brine (15 mL), dried over magnesium sulfate, filtered and concentrated. The crude β-ketoester product was then purified by radial chromatography (4 mm plate, solvent ramp: 100 mL each of 2 %, 4 %, 8 % then 15 % EtOAc / hexanes until the product was recovered) to afford 424 mg of the product **37β** as a yellow oil, in 65 % yield, based on recovered **3** (77 mg): R_f 0.65 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2952, 2870, 1743, 1712, 1492, 1449, 1366, 1318, 1236, 1152, 1096, 1041 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 8.1 Hz, 2H), 7.06 (d, J = 8.2 Hz, 2H), 4.86 (dd, J = 8.0, 5.6 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.26 (d, J_{AB} = 14.0 Hz, 1H), 3.19 (d, J_{AB} = 15.8 Hz, 1H), 3.05 (d, J_{AB} = 15.8 Hz, 1H), 2.32 (s, 3H), 2.29 (d, J_{AB} = 14.0 Hz, 1H), 1.92 – 1.52 (m, 11H) 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 167.3, 138.3, 134.5,

129.5, 129.1, 84.5, 80.2, 61.1, 49.8, 46.4, 41.4, 39.0, 27.4, 25.7, 22.6, 21.8, 21.1, 14.1; HRMS (EI) calcd for $C_{21}H_{28}O_4S$ (M-EtOH$^+$) 330.12897; found 330.12943

Diazoketoester 38β: To a stirred solution of **37β** (91 mg, 0.24 mmol, 1 eq), TEA (34 μL, 0.24 mmol, 1 eq) in CH_3CN (2 mL) was added *p*TsN_3 (48 mg, 0.24 mmol, 1 eq), and the mixture was vigorously stirred at r.t. for 2.5 hours. The CH_3CN was then removed by rotary evaporation and the resulting oil was dissolved in 10 mL of ether. This solution was washed with 5 mL of 25 % aq. KOH, 5 mL of 6 % aq. KOH, then 10 mL water. The organic layer was then dried over sodium sulfate and concentrated by rotary evaporation. The product was purified by radial chromatography (2 mm plate, solvent ramp: 50 mL each of 1 %, 2 %, 5 % then 10 % EtOAc / hexanes until the product was recovered) to afford 54 mg of **38β** as a pale yellow oil in 55 % yield: R_f 0.62 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2948, 2869, 2133, 1712, 1652, 1492, 1371, 1300, 1220, 1145, 1040 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 8.1 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 4.93 (dd, J = 8.0, 5.2 Hz, 1H), 4.21 (q, J = 7.2 Hz, 1H), 4.18 (q, J = 7.2 Hz, 1H), 4.01 (d, J_{AB} = 14.4 Hz, 1H), 2.52 (d, J_{AB} = 14.4 Hz, 1H), 2.31 (s, 3H), 2.13 (m, J = 8.5, 4.7 Hz, 1H), 1.98 – 1.84 (m, 3H), 1.80 – 1.54 (m, 7H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.7, 161.2, 137.5, 133.8, 130.0, 129.1, 85.5, 80.2, 61.3, 41.3, 40.8, 40.0, 27.4, 25.7, 22.8, 22.0, 21.0, 14.3; HRMS (EI) calcd for $C_{21}H_{26}O_4S$ (M-N_2^+) 374.1552; found 374.1548.

Ethyl Acetate Adducts 39α,β: Into a stirring solution of diisopropylamine (409 μL, 2.92 mmol) in THF (1 mL) at –78 °C was added *n*BuLi (1.24 mL of 2.36M solution, 2.92 mmol) and the resulting mixture was stirred at –78 °C for 30 minutes. This was then warmed to 0 °C over several minutes and stirred for another 30 minutes before being cooled once again to –78 °C. Ethyl acetate (280 μL, 2.86 mmol) was added dropwise, and the mixture was stirred for 1 hour. A solution of anomers **25** (183 mg, 0.57 mmol, 1 eq) in THF (1 mL) was added dropwise to the above mixture and the reaction mixture was stirred overnight, allowing the cooling bath to expire. The reaction is then diluted with ethyl ether (10 mL) and quenched by the addition of saturated ammonium chloride solution (5 mL). After separation of the phases, the aqueous layer was extracted with

Et_2O (3 x 5 mL) and the combined organic extracts were washed with water (15 mL) and brine (15 mL), dried over magnesium sulfate, filtered and concentrated. The crude β-ketoester product was then purified by radial chromatography (2 mm plate, solvent ramp: 50 mL each of 2 %, 4 %, 8 % then 15 % EtOAc / hexanes until the product was recovered) to afford the products as yellow oils, as a mixture of separable anomers **39α,β** in 46 % yield (51 and 38 mg, respectively) based on recovered **25** (13 mg).

Major Anomer 39α: R_f 0.69 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2955, 2867, 1744, 1713, 1493, 1446, 1366, 1313, 1235 1153, 1094, 1031 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J = 8.2 Hz, 2H), 7.11 (d, J = 8.2 Hz, 2H), 5.62 (dd, J = 6.2, 6.2 Hz, 1H), 4.16 (q, J = 7.1 Hz, 1H), 4.15 (q, J = 7.1 Hz, 1H), 3.51 (S, 2H), 3.26 (d, J_{AB} = 14.7 Hz, 1H), 2.87 (d, J_{AB} = 14.8 Hz, 1H), 2.62 (m, 1H), 2.32 (s, 3H), 2.27 (ddd, J = 12.7, 8.6, 5.6 Hz, 1H), 1.92 – 1.84 (m, 2H), 1.70 – 1.60 (m, 3H), 1.48 (m, 1H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.1, 167.4, 136.8, 131.9, 130.8 (2C), 129.7 (2C), 95.0, 87.8, 61.1, 52.7, 50.5, 47.4, 40.5, 38.7, 32.7, 24.3, 21.0, 14.1; HRMS (EI) calcd for $C_{20}H_{26}O_4S$ (M^+) 362.1552; found 362.1555.

Minor Anomer 39β: R_f 0.62 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2955, 2867, 1742, 1717, 1493, 1446, 1367, 1305, 1236 1152, 1094, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 7.8 Hz, 2H), 5.30 (dd, J = 6.2, 6.3 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.52 (d, J_{AB} = 15.7 Hz, 1H), 3.46 (d, J_{AB} = 15.7 Hz, 1H), 2.89 (d, J_{AB} = 14.5 Hz, 1H), 2.74 (d, J_{AB} = 14.5 Hz, 1H), 2.62 – 2.50 (m, 2H), 2.32 (s, 3H), 2.00 (m, 1H), 1.80 – 1.52 (m, 6H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 167.2, 137.3, 132.3, 130.8, 129.5, 94.6, 86.4, 61.2, 51.4, 50.5, 47.5, 40.5, 39.0, 33.3, 24.0, 21.1, 14.1; HRMS (EI) calcd for $C_{20}H_{26}O_4S$ (M^+) 362.1552; found 362.1554.

Diazoketone 40α. Ketoester **39α** (50 mg, 0.14 mmol), was subjected to the procedure described above for **38β**, to afford 41 mg of **40α** as a pale yellow oil in 77 % yield: R_f 0.73 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2954, 2867, 2131, 1717, 1652, 1493, 1446, 1370, 1297, 1210, 1057 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 8.1 Hz, 2H),

7.09 (d, J = 7.9 Hz, 2H), 5.51 (dd, J = 6.5, 6.3 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.48 (d, J_{AB} = 16.3 Hz, 1H), 3.44 (d, J_{AB} = 15.9 Hz, 1H), 2.76 (dddd, J = 12.6, 8.3, 4.0, 4.0 Hz, 1H), 2.30 (s, 3H), 2.25 (ddd, J = 14.6, 8.6, 6.1 Hz, 1H), 2.10 (ddd, J = 13.4, 6.6, 4.6 Hz, 1H), 2.04 (m, 1H), 1.89 (m, 1H), 1.72 – 1.56 (m, 3H), 1.47 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.6, 161.3, 136.7, 132.0, 131.5, 129.5, 95.6, 87.8, 61.3, 48.3, 46.7, 40.8, 39.7, 32.9, 24.4, 21.1, 14.3; HRMS (EI) calcd for $C_{20}H_{24}O_4S$ (M-N_2^+) 360.1395; found 360.1390.

Carbene Transfer by Catalytic Decomposition of Diazoketones:

8-Methoxy-12-oxatricyclo[7.2.1.0^{1,5}]undecan-10-one 16β. To a refluxing solution of Cu(hfacac)$_2$ (9.4 mg, 0.02 mmol, 10 mol%) in CH_2Cl_2 (15 mL) was added a solution of **15β** (46.9 mg, 0.20 mmol) in CH_2Cl_2 (5 mL), and the resulting mixture was stirred at reflux until consumption of **15β** (~30 min.), after which the reaction mixture was cooled to room temperature and quenched with 0.5M K_2CO_3 (10 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The organic extracts were combined and washed with water and brine, dried with magnesium sulfate, filtered and concentrated. The crude product was purified by column chromatography (30 % EtOAc / hexanes) to give **16β**, a yellow solid, (34 mg), in 82 % yield: m.p. 41 – 43 °C, R_f 0.44 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2937, 2867, 2823, 1755, 1450, 1403, 1366, 1342, 1299, 1235 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.05 (s, 1H), 3.50 (ddd, J = 6.2, 4.2, 1.2 Hz, 1H), 3.35 (s, 3H), 2.73 (d, J_{AB} = 17.7 Hz, 1H), 2.37 (d, J_{AB} = 17.7 Hz, 1H), 2.09 (m, 1H), 2.02 – 1.92 (m, 2H), 1.89 – 1.81 (m, 2H), 1.79 – 1.71 (m, 2H), 1.66 (m, 1H), 1.56 (m, 1H), 1.48 (ddd, J = 14.5, 10.2, 4.2 Hz, 1H), 1.37 (ddd, J = 13.7, 10.0, 3.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.5, 90.9, 83.1, 81.6, 56.6, 51.3, 49.0, 40.4, 32.1, 27.0, 23.9, 23.5; HRMS (EI) calcd for $C_{12}H_{18}O_3$ (M^+) 210.1256, found 210.1249; Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.60; H, 8.60. Found: C, 68.20; H, 9.06.

Carbene Transfer Reactions of 29α,β; Preparation of 34α,β and 35. To a refluxing solution of Cu(hfacac)$_2$ (37 mg, 0.08 mmol, 10 mol%) in CH_2Cl_2 (55 mL) was added a solution of **29α,β** (168 mg, 0.75 mmol, 4.4:1 mixture of anomers) in CH_2Cl_2 (25 mL),

and the resulting mixture was monitored by T.L.C.. Upon consumption of diazoketones **29α,β** (45 min.) the reaction mixture was cooled to room temperature and quenched with 0.5M K_2CO_3 (25 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 15 mL). The organic extracts were combined and washed with water (20 mL), pre-dried with brine (20 mL), dried with magnesium sulfate, filtered and concentrated. The resulting pale oil was purified by gradient column chromatograhy (silica gel; 5 %, 10 %, 15 % then 20 % EtOAc / hexanes until the products were recovered) to yield **34α** (68 mg) and **34β** (25 mg) as pale yellow oils, in an overall yield of 67 %. (This reaction was also carried out on small scale with pure samples of **29α** and **29β**. **29α** also furnished trace amounts of product **35**.

Major Diastereomer 34α: R_f 0.40 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2938, 2871, 2825, 1760, 1456, 1403, 1370, 1347, 1312 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.04 (d, J = 4.9 Hz, 1H), 3.61 (ddd, J = 10.6, 5.3, 5.3 Hz, 1H), 3.34 (s, 3H), 2.54 (d, J_{AB} = 17.6 Hz, 1H), 2.19 (d, J_{AB} = 17.6 Hz, 1H), 2.06 (dd, J = 13.9, 5.7 Hz, 1H), 1.92 – 1.76 (m, 5H), 1.76 – 1.69 (m, 1H), 1.68 – 1.62 (m, 1H), 1.56 (ddd, J = 13.9, 9.1. 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.4, 88.7, 78.3, 74.7, 56.8, 44.6, 44.4, 34.1, 28.9, 27.5, 21.3; HRMS (ESI) calcd for $C_{11}H_{16}O_3$ (M^+) 196.1099; found 196.1097.

Minor Anomer 34β: R_f 0.46 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2938, 2872, 2824, 1761, 1436, 1405, 1368, 1347, 1312 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.19 (s, 1H), 3.28 (s, 3H), 3.23 (m, 1H), 2.60 (d, J_{AB} = 17.3 Hz, 1H), 2.22 (d, J_{AB} = 17.3 Hz, 1H), 2.03 – 1.74 (m, 7H), 1.66 – 1.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.8, 88.7, 80.3, 75.3, 56.4, 45.3, 41.9, 34.9, 30.9, 26.4, 21.8; HRMS (ESI) calcd for $C_{11}H_{16}O_3$ (M^+) 196.1099; found 196.1092.

Side Product 35 (partial data): ^1H NMR (500 MHz, $CDCl_3$) δ 6.03 (d, J = 2.3 Hz, 1H), 5.56 (d, J = 4.5 Hz, 1H), 3.49 (s, 3H), 2.54 (dd, J = 14.1, 2.3 Hz, 1H), 2.42 (d, J = 14.1 Hz, 1H), 2.33 (dd, J = 13.2, 8.9 Hz, 1H), 2.24 (dddd, J = 9.8, 8.7, 6.4, 4.0 Hz, 1H), 2.01 – 1.83 (m, 3H), 1.74 (app dt, J = 13.2, 4.3 Hz, 1H), 1.70 – 1.56 (m, 2H), 1.35-1.27 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2, 134.0, 102.9, 93.2, 60.1, 44.1, 40.9, 36.0, 34.2, 33.1, 25.7.

Carbene Transfer Reaction of 31α,β; Preparation of 32α,β and 33α,β. To a refluxing solution of $Cu(hfacac)_2$ (16 mg, 0.03 mmol, 10 mol%) in CH_2Cl_2 (33 mL) was added a solution of **31α** (105 mg, 0.33 mmol) in CH_2Cl_2 (8 mL), and the resulting mixture was monitored by T.L.C.. Upon consumption of diazoketone **31α** (30 min.) the reaction mixture was cooled to room temperature and quenched with 0.5M K_2CO_3 (25 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 15 mL). The organic extracts were combined and washed with water (25 mL), pre-dried with brine (25 mL), dried with magnesium sulfate, filtered and concentrated. The resulting pale yellow oil was diluted in ether (20 mL), passed through a short pad of silica gel in a fritted filter, rinsing with excess ether. This was then concentrated and the resulting oil purified by radial chromatography (silica gel, 2 mm plate, solvent ramp: 100 mL each of 2 %, 5 %, 7 % then 10 % EtOAc / hexanes until the products were recovered) to yield 59 mg of **32α,β** a 2:1 mixture in 68 % yield as pale yellow oils, as well as 11 mg of **39α** in 13 % yield as a white solid, in an overall yield of 80 %. Minor diastereomer **32β** could be obtained as a white solid, m.p.: 64 – 65 °C.

Diastereomers 31α,β: R_f 0.41 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 3019, 2955, 2869, 1785, 1711, 1492, 1447, 1401, 1343 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 1H), 7.07 (d, J = 8.1 Hz, 1H), 7.06 (d, J = 8.1 Hz, 2H), 4.01 (s, 0.5H), 3.86 (d, J = 3.9 Hz, 1H), 3.50 (ddd, J = 13.2, 5.4, 4.2 Hz, 1H), 3.27 (ddd, J = 6.9, 13.5, 1.7 Hz, 0.5H), 2.60 (d, J_{AB} = 17.3 Hz, 0.5H), 2.57 (d, J_{AB} = 17.6 Hz, 1H), 2.29 (s, 4.5H), 2.24 (d, J_{AB} = 17.3 Hz, 0.5H), 2.23 (d, J_{AB} = 17.6 Hz, 1H), 2.16 – 2.06 (m, 2H), 1.96 – 1.77 (m, 7.5H), 1.75 – 1.62 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ Major Diast: 213.5, 138.0, 133.3, 130.1, 129.9, 88.5, 79.8, 44.8, 44.5, 44.2, 34.5, 28.1, 27.5, 21.3; Minor Diast: 216.2, 137.8, 132.5, 131.4, 130.2, 89.1, 81.3, 45.8, 45.5, 43.0, 35.5, 31.4, 26.8, 22.3; HRMS (EI) calcd for $C_{17}H_{20}O_2S$ (M^+) 288.1184; found 283.1180; Anal. Calcd for $C_{17}H_{20}O_2S$: C, 70.80; H, 6.99. Found: C, 70.36; H 7.05.

Isomer 33α: m.p. 95 °C; R_f 0.44 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2953, 2866, 1711, 1493, 1448, 1404, 1345, 1301cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 8.0

Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 4.75 (d, J = 7.3 Hz, 1H), 3.43 (d, J_{AB} = 14.8 Hz, 1H), 3.32 (s, 1H), 2.32 (s, 3H), 2.26 – 2.21 (m, 1H), 2.24 (d, J_{AB} = 14.8 Hz, 1H), 2.16 (m, 1H), 2.13 (dd, J = 12.4, 9.1 Hz, 1H), 1.93 – 1.84 (m, 3H), 1.67 (m, 1H), 1.51 (ddd, J = 13.4, 9.8, 7.5 Hz, 1H) , 1.40 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.4, 138.4, 132.9, 130.1, 93.9, 60.9, 48.9, 45.3, 39.9, 37.1, 34.8, 25.4, 21.4; HRMS (EI) calcd for $C_{17}H_{20}O_2S$ (M^+) 288.1184; found 283.1183; Anal. Calcd for $C_{17}H_{20}O_2S$: C, 70.80; H, 6.99. Found: C, 70.90; H, 6.68.

Carbene Transfer Reaction of 31β; Preparation of 32α,β. Diazoketone **31β** was subjected to the procedure above to yield 85 % of **31α,β** in a 1:4.8 ratio. None of the isomeric product **33α** was isolated.

Carbene Transfer Reaction of 38β; Preparation of 41β. To a solution of **38β** (43 mg, 0.11 mmol) in toluene (9 mL) was added $Cu(hfacac)_2$ (9 mg, 0.01 mmol, 10 mol %) and the resulting mixture heated to reflux. Upon consumption of diazoketone **38β** (14 hours at reflux) the reaction mixture was cooled to room temperature and quenched with 0.5M K_2CO_3 (15 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 15 mL). The organic extracts were combined and washed with water (25 mL) and brine (25 mL), dried over magnesium sulfate, filtered and concentrated. The resulting pale oil was diluted in ether (20 mL) and passed through a short pad of silica gel in a fritted filter, rinsing with excess ether. This was then concentrated, and the resulting oil was purified by radial chromatography (2 mm plate, solvent ramp: 50 mL each of 2 %, 5 %, 7 % then 10 % EtOAc / hexanes until the products are recovered) to yield 20 mg of **41β** as a pale oil in 50 % yield (as a 4.5:1 mixture of isomers by G.C..): R_f 0.42 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2952, 2934, 2867, 1769, 1746, 1492, 1443, 1400, 1269, 1254, 1143 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$; major diastereomer) δ 7.34 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 7.9 Hz, 2H), 4.19 (dq, J = 16.4, 7.1 Hz, 1H), 4.15 (dq, J = 16.4, 7.1 Hz, 1H), 4.04 (dd, J = 3.5, 3.5 Hz, 1H), 2.81 (d, J_{AB} = 17.0 Hz, 1H), 2.54 (d, J_{AB} = 17.0 Hz, 1H), 2.35 (m, 3H), 2.32 (s, 3H), 2.18 (dd, J = 11.5, 11.5 Hz, 1H), 2.03 (m, 1H), 1.97 – 1.84 (m, 3H), 1.80 (m, 1H), 1.63 – 1.46 (m, 3H), (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$; major diastereomer) δ 209.1, 166.1, 137.4, 132.4, 131.5, 129.7, 62.3,

55.8, 52.7, 50.8, 41.6, 35.2, 30.1, 26.7, 24.8, 21.1, 13.9; HRMS (EI) calcd for $C_{21}H_{26}O_4S$ (M^+) 374.1552; found 374.1554.

Carbene Transfer Reaction of 40α; Preparation of 41α,β and 43. To a solution of **40α** (122 mg, 0.314 mmol) in toluene (31 mL) was added $Cu(hfacac)_2$ (16 mg, 0.03 mmol, 10 mol %) and the resulting mixture heated to reflux. Upon consumption of diazoketone **40α** (14 hours at reflux) the reaction mixture was cooled to room temperature and quenched with 0.5M K_2CO_3 (25 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 15 mL). The organic extracts were combined and washed with water (25 mL) and brine (25 mL), dried over magnesium sulfate, filtered and concentrated. The resulting pale oil was diluted in ether (20 mL), passed through a short pad of silica gel in a fritted filter, rinsing with excess ether. This was then concentrated and the resulting oil was purified by radial chromatography (2 mm plate, solvent ramp: 50 mL each of 2 %, 5 %, 7 % then 10 % EtOAc / hexanes until the products are recovered) to yield 7 mg of a mixture of **41α,β** (8:1 dr by G.C.) and 48 mg of **43** (single diastereomer by G.C. and NMR) as pale oils (49 % combined yield).

41α: R_f 0.57 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2941, 2871, 1774, 1743, 1493, 1448, 1401, 1342, 1277 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, J = 8.2 Hz, 2H), 7.07 (d, J = 7.9 Hz, 2H), 4.11 (m, 2H), 3.72 (dd, J = 11.4, 6.0 Hz, 1H), 2.78 (d, J_{AB} = 17.4 Hz, 1H), 2.36 (d, J_{AB} = 17.4 Hz, 1H), 2.31 (s, 3H), 2.17 (dd, J = 13.0, 5.9 Hz, 1H), 2.02 – 1.83 (m, 6H), 1.76 - 1.64 (m, 2H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.4, 165.6, 137.7, 133.0, 130.4, 129.7, 87.8. 85.6, 62.1, 46.4, 45.5, 44.1, 34.3, 30.1, 28.5, 21.4, 21.1, 13.8; HRMS (EI) calcd for $C_{20}H_{24}O_4S$ (M^+) 360.1395; found 360.1403.

43: R_f 0.52 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2955, 2869, 1750, 1717, 1492, 1448, 1402, 1346, 1241 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 8.2 Hz, 2H), 4.75 (d, J = 7.0 Hz, 1H), 4.11 (m, 1H), 3.47 (d, J_{AB} = 15.7 Hz, 1H), 2.33 (s, 3H), 2.32 – 2.27 (m, 3H), 2.16 (m, J = 6.0, 2.6 Hz, 1H), 1.93 – 1.82 (m, 3H), 1.68 (m, 1H), 1.52 (ddd, J = 16.9, 9.9, 7.7 Hz, 1H), 1.43 (m, 1H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.3, 166.8, 140.3, 136.3, 129.7, 126.4, 93.9, 81.2,

67.3, 61.6, 48.3, 45.3, 38.6, 36.7, 34.4, 24.9, 21.3, 14.0; HRMS (EI) calcd for $C_{20}H_{24}O_4S$ (M^+) 360.1395; found 360.1397.

Ketalization of 32α,β ; Formation of 44α, β. To a mixture of diastereomers **32α,β** (340 mg, 1.2 mmol, ca. 2.5:1) in CH_2Cl_2 (6 mL) at 0 °C was added 1,2-bis(trimethylsiloxy)ethane (580 μL, 2.4 mmol) followed by TMSOTf (12 μL, 5 mol %) and the resulting mixture was warmed to room temperature over several hours. This was then heated to reflux for ca. 12 hours, after which T.L.C. showed consumption of starting materials. The reaction was quenched with pyridine (1 mL) and saturated aqueous $NaHCO_3$ (5 mL), diluted with Et_2O (10 mL) and the resulting layers were separated. The aqueous layer was washed with 3 portions of Et_2O (10 mL) and the combined organic extracts were washed with water (30 mL) then brine (30 mL), dried over magnesium sulfate, filtered and concentrated, giving the crude product as a yellow oil. This oil was diluted in ether (20 mL) and passed through a short pad of silica gel in a fritted filter, eluting with ether. This was then concentrated and the resulting oil was purified by radial chromatography (silica gel, 2 mm plate, solvent ramp: 100 mL each of 3 %, 6 % then 10 % EtOAc / hexanes until the products are recovered) to yield **41α** (283mg, 72 %) as a pale oil, and **41β** (102 mg, 26 %) as a crystalline solid.

Ketal 44α: R_f 0.63 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2945, 2869, 1492, 1434, 1398, 1344, 1323, 1291 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 4.11 (m, 1H), 4.06 (m, 1H), 3.87, (d, J = 2.6 Hz, 1H), 3.84 (m, 1H), 3.76 (m, 1H), 3.31 (ddd, J = 12.7, 5.8, 3.5 Hz, 1H), 2.37 (d, J_{AB} = 13.7 Hz, 1H), 2.42 – 2.34 (m, 1H), 2.32 (s, 3H), 2.10 (d, J_{AB} = 13.7 Hz, 1H), 2.04 (dd, J = 14.0, 5.7 Hz, 1H), 1.80 – 1.74 (m, 5H), 1.65 – 1.57 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 134.1, 131.1, 130.3, 116.9, 88.5, 83.1, 65.5, 64.6, 45.7, 45.3, 44.9, 34.6, 28.5, 28.4, 21.4, 21.2; HRMS (EI) calcd for $C_{19}H_{24}O_3S$ (M^+) 332.1146; found 332.1438; Anal. Calcd for $C_{19}H_{24}O_3S$: C, 68.64; H, 7.28; S, 9.60. Found: C, 68.78; H, 7.05; S, 9.79.

Ketal 44β: m.p. 78 – 79 °C; R_f 0.54 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2951, 2871, 1492, 1445, 1433, 1398 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J = 8.0 Hz,

2H), 7.05 (d, J = 8.0 Hz, 2H), 3.92 – 3.87 (m, 2H), 3.78 (app q, J = 7.2 Hz, 1H), 3.63 (ddd, J = 11.5, 7.0, 4.5 Hz, 1H), 3.53 (app q, J = 7.4 Hz, 1H), 3.38 (ddd, J = 7.8, 6.1, 1.7 Hz, 1H), 2.29 (s, 3H), 2.24 (d, J_{AB} = 13.4 Hz, 1H), 2.22 (m, 1H), 1.96 (d, J_{AB} = 13.4 Hz, 1H), 1.92 – 1.74 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.2, 132.5, 132.4, 129.9, 116.7, 89.0, 83.4, 65.4, 64.3, 46.1, 44.1 ,43.4, 36.5, 32.1, 27.4, 22.9, 21.3; HRMS (EI) calcd for $C_{19}H_{24}O_3S$ (M^+) 332.1446; found 332.1445; Anal. Calcd for $C_{19}H_{24}O_3S$: C, 68.64; H, 7.28; S, 9.60. Found: C, 68.61; H, 7.01; S, 9.76.

LiDBB Reduction of 44β; Formation of 46, 47 and 48. A large excess of LiDBB was prepared according to Cohen's procedure, using Li (8 mg, 6 equiv) and di-*tert*-butylbiphenyl (300 mg) in THF (3.2 mL). To a solution of **44β** (57 mg, 0.19 mmol) and a crystal of phenanthroline in THF (0.7 mL) cooled to –78 °C was added *n*BuLi until the color turned deep red. LiDBB was then added dropwise (without quantification) to the reaction mixture until the intense green color persisted, indicating the presence of excess LiDBB. The reaction was stirred until consumption of starting material was observed by T.L.C. (ca. 2 hours). The reaction was then quenched by addition of saturated aqueous ammonium chloride (5 mL), further diluted in Et_2O (15 mL), and the resulting bi-layer was separated. The aqueous layer was back extracted once with Et_2O (10 mL) and the combined organic extracts were pre-dried with brine (30 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was purified by gradient column chromatography (silica gel, 0 %, 20 %, 60 % EtOAc / hexanes) to give **46** (25 mg, 69 %) as a pale yellow oil, as well as a trace of isomer **47** (2 mg, 5.5 %), in an overall yield of 75 %. The ratio of product isomers depended on the time allowed for the reaction: if the reaction was quenched after 30 minutes, the ratio of the products is **46** (19 %) and isomer **47** (45 %).

Alcohol 46: R_f 0.36 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 3513, 3025, 2959, 1653, 1445, 1425, 1397, 1344, 1316, 1281 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (ddd, J = 12.2, 8.9, 3.5 Hz, 1H), 5.65 (ddd, J = 12.0, 3.1, 1.3 Hz, 1H), 4.19 (s, 1H) 3.93 (s, 4H), 2.29 (dddd, J = 16.1, 11.8, 3.1, 3.1 Hz, 1H), 2.21 (d, J_{AB} = 14.1 Hz, 1H), 2.04 (ddd, J = 16.0, 8.8, 2.3 Hz, 1H), 1.86 (d, J_{AB} = 14.1 Hz, 1H), 1.80 – 1.66 (m, 3H), 1.65 – 1.50 (m,

4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.9, 133.6, 108.6, 78.6, 64.6, 63.9, 47.2, 44.9, 41.9, 30.9, 26.6, 19.8; HRMS (ESI) calcd for $C_{12}H_{18}O_3Na$ (M^+) 233.1148; found 233.1149.

Isomer 47: R_f 0.09 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 3428 (br), 2946, 2865, 1651, 1446, 1433, 1360, 1327 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.79 (d, J = 4.9 Hz, 1H), 4.53 (t, J = 5.2 Hz, 1H), 3.83 – 3.78 (m, 2H), 3.76 – 3.67 (m, 2H), 2.71 (d, J_{AB} = 16.3 Hz, 1H), 2.35 (m, 1H), 2.27 (dd, J = 11.2, 8.8 Hz, 1H), 1.94 (m, 1H), 1.90 (d, J_{AB} = 16.2 Hz, 1H), 1.85 (m, 1H), 1.83 – 1.73 (m, 2H), 1.66 – 1.56 (m, 2H), 1.44 – 1.36 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 99.4, 90.8, 74.1, 67.8, 61.3, 46.0, 46.9, 39.9, 37.1, 33.0, 24.8; HRMS (EI) calcd for $C_{12}H_{18}O_3$ (M^+) 210.1256; found 210.1253.

Isomer **47** was found to reketalize upon standing in $CDCl_3$ to give compound **48**: R_f 0.40 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2951, 2869, 1350 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.43 (dd, J = 7.6, 4.3 Hz, 1H), 3.92 (2^{nd} order app t, J = 6.3 Hz, 2H), 3.81 (2^{nd} order app t, J = 6.3 Hz, 2H), 2.67 (app tt, J = 9.2, 4.7 Hz, 1H), 2.31 (dd, J = 12.2, 9.0 Hz, 1H), 2.08 (d, J_{AB} = 13.5 Hz, 1H), 1.96 – 1.86 (m, 2H), 1.86 – 1.78 (m, 2H), 1.72 (dd, J = 13.5, 2.0 Hz, 1H), 1.65 – 1.61 (m, 1H), 1.64 (ddd, J = 13.8, 1.8, 1.8 Hz, 1H), 1.56 – 1.51 (m, 1H), 1.45 – 1.40 (m, 1H), 1.35 – 1.30 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 107.6, 91.5, 76.0, 64.3, 63.2, 44.5, 44.2, 40.7, 39.0, 37.4, 34.9, 25.1; HRMS (EI) calcd for $C_{12}H_{18}O_3$ (M^+) 210.1256; found 210.1253.

2.6. References

1. Mehta, G.; Singh, V., Progress in the Construction of Cyclooctanoid Systems: New Approaches and Applications to Natural Product Syntheses. *Chem. Rev.* **1999,** 99, (3), 881-930.

2. Chiu, P.; Lautens, M., Using Ring-Opening Reactions of Oxabicyclic Compounds as a Strategy in Organic Synthesis. *Top. Curr. Chem.* **1997**, 190, 1-85.

3. Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J., Asymmetric Cyclopropanations by Rhodium(II) N-(Arylsulfonyl)Prolinate Catalyzed Decomposition of Vinyldiazomethanes in the Presence of Alkenes. Practical Enantioselective Synthesis of the Four Stereoisomers of 2-Phenylcyclopropan-1-Amino Acid. *J. Am. Chem. Soc.* **1996,** 118, (29), 6897-6907.

4. De Armas, P.; Garcia-Tellado, F.; Marrero-Tellado, J. J., Enantioselective Synthesis of Medium-Sized Ring-Bridged Oxabicycles by Ring-Closing Metathesis. *Eur. J. Org. Chem.* **2001**, (23), 4423-4429.

5. Lee, K.; Cha, J. K., Synthetic Studies on [4+3] Cycloadditions of Oxyallyls, Part 14 - Formal Synthesis of (+)-Phorbol. *J. Am. Chem. Soc.* **2001,** 123, (23), 5590-5591.

6. Lopez, F.; Castedo, L.; Mascarenas, J. L., A Practical Route to Enantiopure, Highly Functionalized Seven-Membered Carbocycles and Tetrahydrofurans: Concise Synthesis of (+)-Nemorensic Acid. *Chem.-Eur. J.* **2002,** 8, (4), 884-899.

7. Wender, P. A.; Rice, K. D.; Schnute, M. E., The First Formal Asymmetric Synthesis of Phorbol. *J. Am. Chem. Soc.* **1997,** 119, (33), 7897-7898.

8. Williams, D. R.; Benbow, J. W.; Mcnutt, J. G.; Allen, E. E., Functionalization and Utility of Bridging Ethers in the Transformations of Bicyclo[5.4.0]Undecanes. *J. Org. Chem.* **1995,** 60, (4), 833-843.

9. Molander, G. A.; Eastwood, P. R., Total Synthesis of (+)-Dactylol Via a Novel [3+5]-Annulation Approach. *J. Org. Chem.* **1995,** 60, (14), 4559-4565.

10. Rigby, J. H.; Wilson, J. A. Z., A General-Approach to the Synthesis of C-8-Oxygenated Guaianolides. *J. Org. Chem.* **1987,** 52, (1), 34-44.

11. Harmata, M.; Rashatasakhon, P., Intramolecular 4+3 Cycloadditions. Aspects of Stereocontrol in the Synthesis of Cyclooctanoids. A Synthesis of (+)-Dactylol. *Org. Lett.* **2000,** 2, (18), 2913-2915.

12. Tester, R. W.; West, F. G., Medium Ring Ethers Via [1,2]-Shift of Acetal-Derived Oxonium Ylides. *Tetrahedron Lett.* **1998,** 39, (26), 4631-4634.

13. West, F. G.; Eberlein, T. H.; Tester, R. W., O-Bridged Medium-Sized Rings Via Bicyclic Oxonium Ylides. *J. Chem. Soc., Perkin Trans. 1* **1993,** (23), 2857-2859.

14. Oku, A.; Numata, M., Three- to Six-Carbon Ring-Enlargement Reaction of Cyclic Ortho Esters Bearing a Diazocarbonyl Side Chain. Use of the Intramolecular Formation of Tricyclooxonium Ylides. *J. Org. Chem.* **2000,** 65, (7), 1899-1906.

15. Oku, A.; Ohki, S.; Yoshida, T.; Kimura, K., Three-Carbon Ring-Enlargement of Ethereal Oxonium Ylides - a Viable Synthesis of Medium-Sized Cyclic Ketoethers. *Chem. Commun.* **1996,** (9), 1077-1078.

16. Clark, J. S.; Walls, S. B.; Wilson, C.; East, S. P.; Drysdale, M. J., Construction of Fused Medium-Ring Carbocycles by Catalytic Generation and Rearrangement of Oxonium Ylides. *Eur. J. Org. Chem.* **2006,** (2), 323-327.

17. Roskamp, E. J.; Johnson, C. R., Generation and Rearrangements of Oxonium Ylides. *J. Am. Chem. Soc.* **1986,** 108, (19), 6062-6063.

18. Brogan, J. B.; Bauer, C. B.; Rogers, R. D.; Zercher, C. K., Selectivity in the Rearrangements of Oxonium Ylides. *Tetrahedron Lett.* **1996,** 37, (29), 5053-5056.

19. Brogan, J. B.; Zercher, C. K.; Bauer, C. B.; Rogers, R. D., Study of the Rearrangements of Oxonium Ylides Generated from Ketals. *J. Org. Chem.* **1997,** 62, (12), 3902-3909.

20. Marmsäter, F. P. Generation and Rearrangements of Oxonium Ylides in Synthesis. The University of Utah, Utah, 2003.

21. Ando, S.; Minor, K. P.; Overman, L. E., Ring-Enlarging Cyclohexane Annulations. *J. Org. Chem.* **1997,** 62, (18), 6379-6387.

22. Eberlein, T. H.; West, F. G.; Tester, R. W., The Stevens [1,2]-Shift of Oxonium Ylides - a Route to Substituted Tetrahydrofuranones. *J. Org. Chem.* **1992,** 57, (12), 3479-3482.

23. Marmsäter, F. P.; Vanecko, J. A.; West, F. G., Cyclic Oxonium Ylides: Building Blocks for Iterative Synthesis of Polycyclic Ethers. *Tetrahedron* **2002,** 58, (10), 2027-2040.

24. Marmsäter, F. P.; West, F. G., Iterative Approach to Polycyclic Ethers Based on Stereoselective Oxonium Ylide [2,3]-Shifts. *J. Am. Chem. Soc.* **2001,** 123, (21), 5144-5145.

25. West, F. G.; Naidu, B. N.; Tester, R. W., Profound Catalyst Effects in the Generation and Reactivity of Carbenoid-Derived Cyclic Ylides. *J. Org. Chem.* **1994,** 59, (23), 6892-6894.

26. Hashimoto, S.; Watanabe, N.; Anada, M.; Ikegami, S., Site- and Enantiocontrol in Intramolecular C-H Insertion Reactions of Alpha-Diazo Carbonyl Compounds Catalyzed by Dirhodium(II) Carboxylates. *J. Syn. Org. Chem. Jpn.* **1996,** 54, (11), 988-999.

27. Hashimoto, S.; Watanabe, N.; Ikegami, S., Highly Selective Insertion into Aromatic C-H Bonds in Rhodium(Ii) Triphenylacetate-Catalyzed Decomposition of Alpha-Diazocarbonyl Compounds. *J. Chem. Soc., Chem. Commun.* **1992**, (20), 1508-1510.

28. Hashimoto, S.; Watanabe, N.; Ikegami, S., Dirhodium(II) Tetra(Triphenylacetate) - a Highly Efficient Catalyst for the Site-Selective Intramolecular C-H Insertion Reactions of Alpha-Diazo Beta-Keto-Esters. *Tetrahedron Lett.* **1992,** 33, (19), 2709-2712.

29. Marmsäter, F. P.; Vanecko, J. A.; West, F. G., Catalyst and Ring Size Effects on Periselectivity of Oxonium Ylide Rearrangements. *Org. Lett.* **2004,** 6, (10), 1657-1660.

30. Silverstein, R. M.; Webster, F. X., *Spectrometric Identification of Organic Compounds*. 6 ed.; Wiley: 1998; p 482.

31. Ollis, W. D.; Rey, M.; Sutherland, I. O., Base-Catalyzed Rearrangements Involving Ylide Intermediates .15. The Mechanism of the Stevens [1,2] Rearrangement. *J. Chem. Soc., Perkin Trans. 1* **1983,** (5), 1009-1027.

32. Stella, L.; Janousek, Z.; Merenyi, R.; Viehe, H. G., Stabilization of Radicals by Capto-Dative Substitution-C-C Addition to Radicophilic Olefins. *Angew. Chem., Int. Ed.* **1978,** 17, (9), 691-692.

33. Viehe, H. G.; Janousek, Z.; Merenyi, R.; Stella, L., The Captodative Effect. *Acc. Chem. Res.* **1985,** 18, (5), 148-154.

34. Viehe, H. G.; Merenyi, R.; Stella, L.; Janousek, Z., Capto-Dative Substitution Effects .5. Capto-Dative Substituent Effects in Syntheses with Radicals and Radicophiles. *Angew. Chem., Int. Ed.* **1979**, 18, (12), 917-932.

35. Hirst, G. C.; Howard, P. N.; Overman, L. E., Stereocontrolled Construction of Carbocyclic Rings by Sequential Cationic Cyclization Pinacol Rearrangements. *J. Am. Chem. Soc.* **1989,** 111, (4), 1514-1515.

36. Johnson, T. O., Jr. Ring-Enlarging Cyclopentene Annulations and Total Syntheses of the *Lycopodium* Alkaloids Magellanine and Magellanone. University of California, Irvine, 1992.

37. Pirrung, M. C.; Werner, J. A., Intramolecular Generation and [2,3]-Sigmatropic Rearrangement of Oxonium Ylides. *J. Am. Chem. Soc.* **1986,** 108, (19), 6060-6062.

38. Aggarwal, V. K.; Harvey, J. N.; Robiette, R., On the Importance of Leaving Group Ability in Reactions of Ammonium, Oxonium, Phosphonium, and Sulfonium Ylides. *Angew. Chem., Int. Ed. Engl.* **2005,** 44, (34), 5468-5471.

39. Huckin, S. N.; Weiler, L., Alkylation of Dianions of Beta-Keto-Esters. *J. Am. Chem. Soc.* **1974,** 96, (4), 1082-1087.

40. Doyle, M. P.; Mckervey, M. A.; Ye, T., *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*. Wiley-Interscience: New York, 1997; p 652.

41. Cohen, T.; Bhupathy, M., Organoalkali Compounds by Radical-Anion Induced Reductive Metalation of Phenyl Thioethers. *Acc. Chem. Res.* **1989,** 22, (4), 152-161.

42. Rychnovsky, S. D.; Buckmelter, A. J.; Dahanukar, V. H.; Skalitzky, D. J., Synthesis, Equilibration, and Coupling of 4-Lithio-1,3-Dioxanes: Synthons for Syn- and Anti-1,3-Diols. *J. Org. Chem.* **1999,** 64, (18), 6849-6860.

43. Paquette, L. A.; Reagan, J.; Schreiber, S. L.; Teleha, C. A., Intramolecular Sn' Cleavage of Allylic Ethers by Enolate Anions. *J. Am. Chem. Soc.* **1989,** 111, (6), 2331-2332.

3. Chapter 3

In Situ Generated Iodonium Ylides as Carbene Transfer Reagents

3.1. Introduction

Even with the wide variety of reactive pathways associated with the formation of metallocarbenes from diazoketones, adoption of metallocarbene-based methods has not found the sort of widespread use one would expect for such versatile chemistry. Possible reasons include the toxicity of the diazotransfer reagents, as well as the explosive hazards associated with the formation of diazoketones. Several approaches have been investigated to circumvent the formation of diazoketones while providing the metallocarbene directly from simple starting materials. These include thermolysis of hydrazone salts[1,2] or in situ diazotization[3] in the presence of catalyst. One approach, carbene transfer from iodonium ylides, has found significant exposure in recent times. Iodonium ylides are easily prepared from both C-H and N-H acidic compounds, and undergo carbene transfer upon exposure to a transition metal catalyst. This protocol has been shown to afford the products of carbenoid pathways in similar yields as the corresponding diazo-mediated reactions. Carbene transfer from in situ generated iodonium ylides has been employed in cyclopropanation[4-7] or aziridination,[4,8-11] C-H insertion[12] as well as the generation or carbonyl ylides[13] and their cycloadditions. Surprisingly, it had not been applied to the generation of onium ylides prior to this work. This chapter will discuss the in situ synthesis of iodonium ylides, their carbene transfer to rhodium and copper catalysts and the subsequent formation and rearrangement of oxonium and sulfonium ylides.

3.2. Background

Organic compounds of hypervalent iodine are becoming quite common in organic chemistry. The I^V reagents react as oxidants, readily oxidizing simple alcohols, and the most common of these is the oxidant Dess-Martin periodinane (Figure 1).[14] Another such oxidant is IBX, which is known to effect simple oxidations as well, along with other interesting reactions (Figure 1).[15-17] There are also many I^{III} based oxidants, including the series of derivatized iodosobenzenes (Figure 3.1). The most common of these are bis(acetoxy)iodobenzene (DAIB) and bis(trifluoroacetoxy)iodobenzene (DTFAIB). The chemical versatility of these compounds is extensive. Reactions that are commonly observed include the dihydroxybenzene to 1,4-benzoquinone oxidation,[18] the nucleophilic trapping of phenols,[19-21] the α-hydroxylation[22] or α-substitution[23] of enolizable ketones as well as the Pummerer-type reactions of α-acylsulfides (Figure 3.2).[24] These I^{III} reagents have also been shown to readily afford iodonium ylides upon treatment with C-H acidic, β-dicarbonyl compounds in the presence of base.[25,26] Though the ylides formed can be stable, isolation and purification can be difficult.

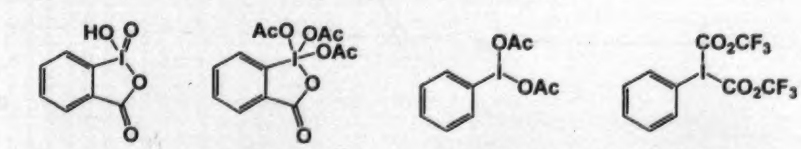


Figure 3.1: Structures of common I^V and I^{III} oxidizing agents IBX, DMP, DAIB and DTFAIB.

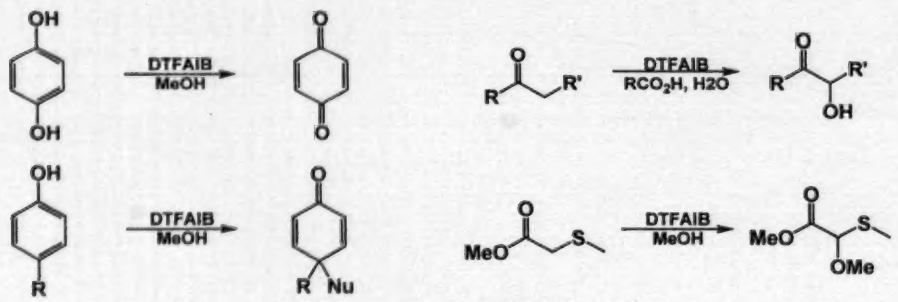
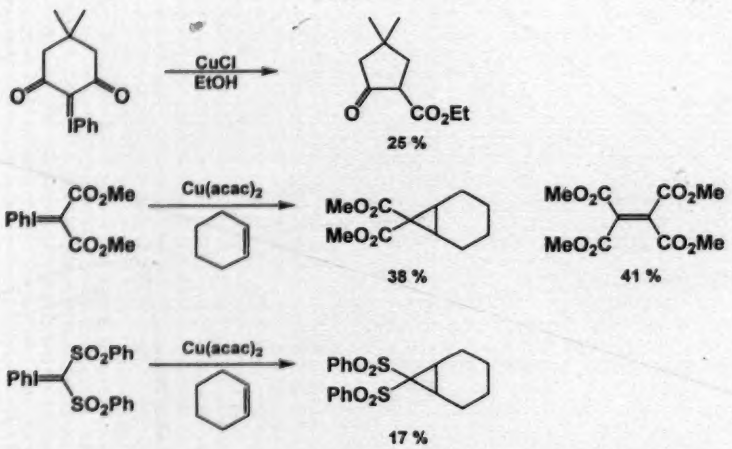


Figure 3.2: Reactions common to the I^{III} oxidizing agents.

The first iodonium ylide was synthesized by Neiland in 1957.[27] Subsequent to this, there were several preliminary reports of iodonium ylides being treated with transition metal catalysts, affording the products of carbenoid pathways (Scheme 3.1).[28-30] It was poorly understood whether or not the catalyst was simply acting as a carbene transfer agent, then dissociating to afford a "free" carbene, or whether the reaction proceeded by way of a metallocarbene intermediate. In all of the early cases, the products isolated are known to occur from "free" carbenoid processes, commonly affording mixtures of the desired product and the carbenoid dimers in intermolecular cases.



Scheme 3.1: Early reports of carbenoid processes from iodonium ylides.

The research groups of Moriarty[25] and Varvoglis[31] have devoted a significant amount of research efforts toward the chemistry of hypervalent iodine reagents. Moriarty and co-workers questioned the role of catalyst in the carbene transfer of iodonium ylides by investigating the intramolecular cyclopropanation process. What they found was that the catalyst was accelerating the reaction, but there was also a slower, uncatalyzed background reaction. Others have also sought to determine the effect of catalyst in iodonium ylide-mediated carbenoid processes. In a competition study by Müller, both diazoketones and iodonium ylides of the same substrates were treated under the same conditions, using chiral catalysts.[32] They found identical selectivities for diazo- and iodonium ylide-mediated reactions employing chiral Rh (II) and Cu (I) catalysts, which strongly supported the involvement of a metallocarbene intermediate. Based on the proposed formation of a common metallocarbene intermediate, the following reaction sequence is likely operative (Figure 3.3). The initial substrate is converted into either a diazoketone or an iodonium ylide, which undergoes metallocarbene formation upon treatment with a transition metal catalyst. Based on the nature of the substitutent (G) the metallocarbene can react through numerous carbenoid processes, including C-H insertion, cyclopropanation, carbonyl ylide formation and so on.

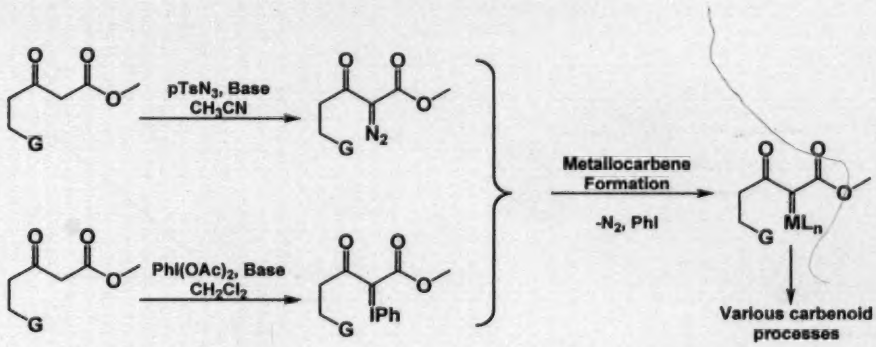


Figure 3.3: The reaction sequence of diazo- or iodonium ylide-mediated carbenoid processes.

There are numerous examples in the literature of the various carbenoid processes occurring via the intermediacy of iodonium ylides. Dauban,[4] Müller[33] and Charette[6,7] have investigated the cyclopropanation of olefins via this protocol. DeLuca and co-workers have demonstrated the effective C-H insertion mediated by iodonium ylides.[12] Müller has shown that ylides can be formed by a carbonyl intercepting a metallocarbene, and that these resulting ylides can undergo subsequent cycloadditions.[13]

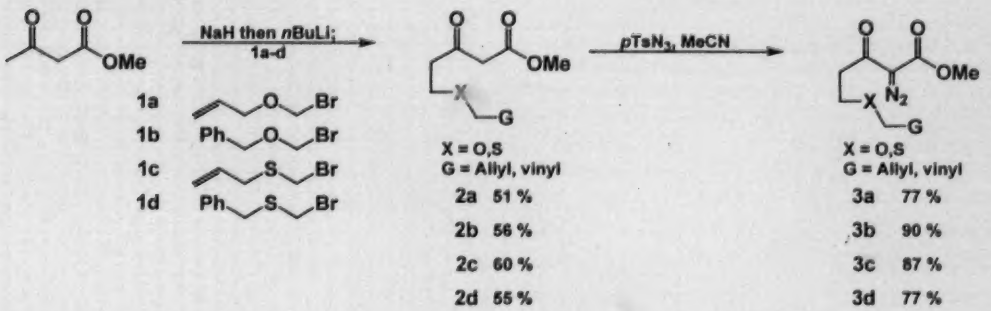
Missing from these examples is the generation of metallocarbenes from iodonium ylide intermediates, and their subsequent capture by heteroatoms that are appropriately substituted for the resulting onium ylides to undergo further rearrangements. Our research group has demonstrated the synthesis of functionalized heterocycles through the rearrangements of oxonium ylides, affording numerous structural motifs. [34-38] The substrates in these studies were typically mono-stabilized or di-stabilized diazoketones. The synthesis of the former can be difficult and gives rise to unwanted side products. The latter are prepared by diazotransfer, which is often a facile and high yielding process. There is limited use of mono-stabilized iodonium ylides in synthesis as they cannot be formed in situ, and must be generated from pre-formed masked ylides.[39,40] Conversely, di-stabilized iodonium ylides can be generated in situ, so we chose to use substrates amenable to this protocol for our investigation.

Our goal was to develop a one-pot protocol for the in situ generation of phenyliodonium ylides in the presence of a transition metal catalyst. The ylides would then undergo carbene transfer, and make onium ylides of pendant ethers or sulfides. These onium ylides would be designed to undergo either [1,2]- or [2,3]-shift (depending on substitution). This would also be a competition study in that the analogous diazo substrates would also be treated with the same catalysts, and the results of each investigation compared. We also planned to attempt the asymmetric induction into substrates undergoing [2,3]-rearrangement using both of the one-pot and two-step protocols to determine its feasibility.

3.3. Results and Discussion

3.3.1. Synthesis and rearrangement of the diazo substrates.

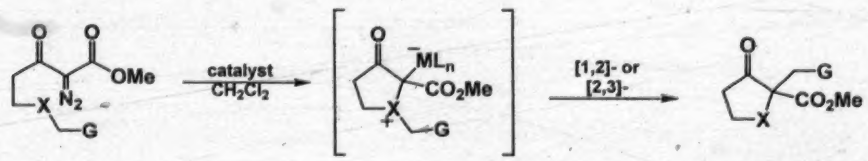
To test the feasibility of carbene transfer from iodonium ylides in the [1,2]- or [2,3]-rearrangement of oxonium and sulfonium ylides, we prepared a series of simple allyl and benzyl-substituted ethers and sulfides. To enable formation of either the diazoketone or the iodonium ylides, the substrates were designed to have an acidic methylene, flanked by two carbonyls. Toward this end, methyl acetoacetate was treated with sodium hydride, then *n*-BuLi to give the dianion[41] which was alkylated with a series of allyl- and benzyl-substituted bromomethyl ethers and sulfides (**1a-d**)[42,43] to give **2a-d** in moderate yield (Scheme 3.2). The corresponding diazoketones **3a-d** were prepared by standard diazotransfer conditions.[44]



Scheme 3.2: Synthesis of the substrates to undergo iodonium ylide-mediated (**2a-d**) and diazoketone-mediated (**3a-d**) carbene transfer and rearrangement.

Diazoketones **3a-d** were treated with $Rh_2(OAc)_4$ and $Cu(hfacac)_2$, catalysts that have been shown in previous studies to be highly effective in the generation and rearrangement of onium ylides.[45] Substrate **3a** afforded the desired product in 88 % under rhodium catalysis, and in 99 % under copper catalysis, in short reaction time (Table 3.1, entries 1,2). Benzyl ether substrate **3b** underwent ylide formation and [1,2]-shift in moderate yield (< 40 %) regardless of catalyst employed (entries 3,4). Though this yield was lower

than expected, it is consistent with what others have previously observed regarding the relative efficiencies of the [1,2]- vs [2,3]-shift.[36,46,47]



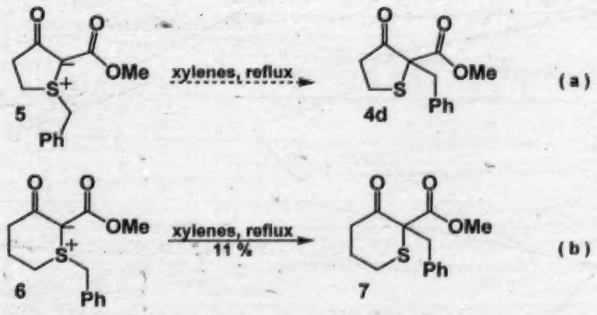
entry	substrate	G	X	catalyst	time (h)	product (% yield)
1	**3a**	allyl	O	$Rh_2(OAc)_4$	0.2	**4a** (88)
2	**3a**	allyl	O	$Cu(hfacac)_2$	1	**4a** (99)
3	**3b**	Ph	O	$Rh_2(OAc)_4$	1	**4b** (39)
4	**3b**	Ph	O	$Cu(hfacac)_2$	16	**4b** (34)
5	**3c**	allyl	S	$Rh_2(OAc)_4$	24	**4c** (63)
6	**3c**	allyl	S	$Cu(hfacac)_2$	24	**4c** (89)
7	**3d**	Ph	S	$Rh_2(OAc)_4$	24	**5**
8	**3d**	Ph	S	$Cu(hfacac)_2$	24	**5**

Table 3.1: The diazoketone-mediated [1,2]- and [2,3]-shifts of oxonium and sulfonium ylides.

The allyl and benzyl sulfides were subsequently treated by the same means. Allyl sulfide **3c** underwent rearrangement to give **4c** in 63 % yield with rhodium acetate and 89 % under copper catalysis (entries 5,6). These reactions required extended reaction times, as the sulfonium ylides formed are more stable than the corresponding oxonium ylides[48] and rearrange more slowly. The yield of the rhodium-catalyzed reaction was lower than expected, and this may be due to catalyst deactivation by the sulfide.[49,50] It was observed upon addition of the catalyst to the reaction mixture that the colour changed from green to pink, presumably due to sulfide coordination. While carbene transfer from diazoketones is typically fast, substrate **3b** could be recovered in quantitative yield from

the reaction mixture after one hour, a time in which carbenoid processes are typically done.

Lengthy reaction times were also required with benzyl sulfide **3d**, the reaction requiring 24 hours to consume the starting material. In this case, however, none of the [1,2]-shift product **4d** was recovered; the reaction afforded only the stable sulfonium ylide **5** under both rhodium and copper catalysis (entries 7,8). The lack of reactivity of this ylide may be due to a combination of the energy required for bond homolysis to occur, as well as the lower reactivity of sulfonium ylides due to their stability. We initially presumed that this reaction failed as a result of being conducted at room temperature. The reaction was repeated in refluxing toluene, but again only the sulfonium ylide was observed by G.C. analysis. As a last effort, we heated a sample of the pure ylide in refluxing xylenes, and analyzed the reaction by G.C., which still only showed the unreacted ylide **5**. The lack of reactivity of this ylide is consistent with the results of Moody[51] on the homologous substrate **6** (Scheme 3.3). The 6-membered sulfonium ylide was heated in refluxing xylenes, and the [1,2]-shift product **7** was isolated in only 11 % yield.



Scheme 3.3: Stable sulfonium ylides isolated from carbene reactions.

3.3.2. The iodonium ylide mediated shifts

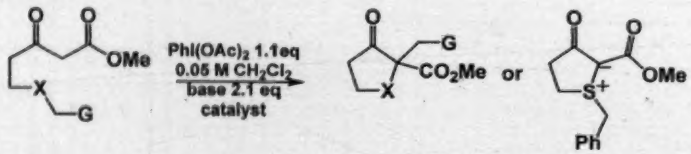
Using the above results as a baseline, we set out to develop the conditions for in situ iodonium ylide formation. The initial investigation using substrate **2a** employed

conditions previously shown to afford in situ iodonium ylide formation in other carbenoid processes (Table 3.2).[33,52] We found that treatment of **2a** with bis(acetoxy)iodobenzene (DAIB) in methanol with potassium hydroxide in the presence of rhodium acetate afforded **4a** in 55 % yield. We were pleased to find that the reaction was successful, though the yield of the reaction was inferior to that found for the two-step (diazo-mediated) process.

Optimization of the reaction conditions included changing the solvent (entry 2) and the base employed. Using CH_2Cl_2 as the solvent gave **4a** in 63 % yield, while changing the base to K_2CO_3 gave **4a** in 67 % yield (entry 4). The base was again changed to Cs_2CO_3, on the assumption that its greater solubility in organic solvents might be to our benefit, and **4a** was isolated in 80 % yield. We also believed that using the more electrophilic bis(trifluoroacetoxy)iodobenzene (DTFAIB) might afford a greater yield of **4a**, but in the event none of **4a** was isolated from the reaction mixture (entry 5). From these trials, the optimal CH_2Cl_2 and Cs_2CO_3 protocol would serve as the standard reaction conditions for the remaining trials, as it afforded **4a** from **2a** in 12 % greater yield than did the two-step protocol. Two additional experiments were conducted to determine the effect of catalyst. We ran one trial as a control experiment without catalyst to determine if there was a background uncatalyzed reaction as is known for the iodonium ylide-mediated cyclopropanation of olefins (entry 6). Indeed, treatment of **2a** in new glassware with base and DAIB afforded small quantities of the desired product. Similar to the cyclopropanation of olefins, there appears to be an uncatalyzed background reaction in the rearrangement of oxonium ylides. As a final catalyst investigation, $Cu(hfacac)_2$ was employed in the reaction, but product **4a** was only isolated in 9 % yield over 10 hours, in stark contrast to the copper-mediated diazoketone process which gave **4a** in 99 % yield (entry 7).

The remaining three substrates were treated under these optimal conditions, employing both the rhodium and copper catalysts for comparison. The benzyl ether substrate **2b** gave product **4b** in 41 % yield under rhodium catalysis (entry 9). Under copper catalysis, none of the desired product was isolated from the reaction (entry 10).

The allyl sulfide catalyst **2c** gave product **4c** in 78 % yield over 19 hours under rhodium catalysis (entry 11), and in only 32 % yield over 64 hours under copper catalysis (entry 12). Lastly, the benzyl sulfide **2d** was treated under these reaction conditions, employing both rhodium and copper catalysts (entries 13,14), but none of **4d** was isolated regardless of reaction time, affording only the stable sulfonium ylide **5**.



entry	substrate	base	catalyst	time (h)	product (% yield)	two-step yield
1[a]	**2a**	KOH	$Rh_2(OAc)_4$	1.5	**4a** (55)	68
2	**2a**	KOH	$Rh_2(OAc)_4$	8	**4a** (63)	68
3	**2a**	K_2CO_3	$Rh_2(OAc)_4$	3	**4a** (70)	68
4	**2a**	Cs_2CO_3	$Rh_2(OAc)_4$	12	**4a** (80)	68
5[b]	**2a**	Cs_2CO_3	$Rh_2(OAc)_4$	7d	**4a** (-)	68
6	**2a**	Cs_2CO_3	-	16	**4a** (N/A)[c]	-
7	**2a**	Cs_2CO_3	$Cu(hfacac)_2$	10	**4a** (9)	77
8	**2a**	Cs_2CO_3	CuBr	24	**4a** (6)	-
9	**2b**	Cs_2CO_3	$Rh_2(OAc)_4$	0.5	**4b** (41)	35
10	**2b**	Cs_2CO_3	$Cu(hfacac)_2$	12	**4b** (-)	31
11	**2c**	Cs_2CO_3	$Rh_2(OAc)_4$	19	**4c** (78)	55
12	**2c**	Cs_2CO_3	$Cu(hfacac)_2$	64	**4c** (32)	77
13	**2d**	Cs_2CO_3	$Rh_2(OAc)_4$	24	**5**	
14	**2d**	Cs_2CO_3	$Cu(hfacac)_2$	14	**5**	

[a] : reaction carried out in methanol; [b] : bis(trifluoroacetoxy)iodobenzene was used as the I^{III} reagent; [c] : formation of the product was only confirmed by G.C. analysis.

Table 3.2: The iodonium ylide-mediated [1,2]- and [2,3]-shifts of oxonium and sulfonium ylides.

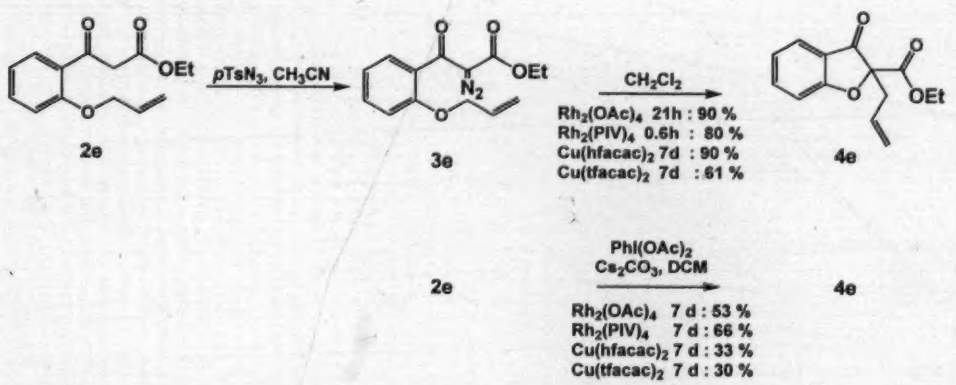
In summary, the one-pot protocol has afforded the [1,2]- or [2,3]-shift products in greater yield than the two-step diazo protocol. The rearrangement products of **2a** and **2c** were isolated in 12 % (**2a**) and 23 % (**2c**) greater yield than the diazo method. The [1,2]-shift processes were found to be lower yielding than the [2,3]-shifts, though the one-pot process still afforded **4b** (from **2b**) in 6 % greater yield than the two-step process. For substrate **2d**, the ylide was recovered in all cases. Even upon prolonged heating, ylide **5** failed to undergo the [1,2]-shift, likely a result of the greater stability of the ylide, as well as the higher energy barrier of bond homolysis necessary for the shift.

Interesting chemoselectivity was also observed in the one-pot process for substrates **2c,d**. It has been shown that treatment of sulfides with organic trivalent iodine compounds (DAIB or DTFAIB) can result in S-oxidation, affording Pummerer-type reactivities.[24,53] We were originally concerned that this might be a competitive side process during the in situ iodonium ylide formation. We were pleased to find none of the sulfoxide products were observed in any trial employing the substrates **2c,d**. We believe this to not be a competitive process in the weakly basic, anhydrous reaction conditions found to be optimal for the one-pot protocol.

We further found that copper catalysis was poorly effective at promoting the shifts in the one-pot protocol. Given that the active catalyst in copper-catalyzed carbenoid processes is copper I, it has been suggested that copper II catalysts are reduced to copper I in the reaction with diazoketones, presumably from a sacrificial quantity of the diazo substrate.[54-56] The absence of any diazoketone, or other molecule, that could reduce the copper II catalyst may account for the low yields and prolonged reaction times of the copper-mediated reactions. In addition, it is also possible that the oxidant DAIB has a greater reduction potential than that of copper II. Were this so, it would have made the reductive activation of the catalyst less likely, further contributing to the low yield. One trial reaction was attempted using the copper I catalyst CuBr, but very little of **4a** was recovered from the reaction mixture (Table 2, entry 8).

3.3.3. The iodonium ylide-mediated rearrangement of an aromatic substrate

With the favorable results observed from the aliphatic [2,3]-rearrangements, we set out to also determine the feasibility of the one-pot protocol for the rearrangement of aromatic-fused substrate **2e**. This known[57] substrate was converted to the diazoketone using the diazotransfer protocol, and this underwent efficient conversion to **4e** upon treatment with either rhodium or copper catalysts (Scheme 3.4). The ketoester **2e** was treated with the standard one-pot reaction conditions with various catalysts, which afforded product **4e** in moderate yields over prolonged reaction times in all cases. In contrast to the analogous aliphatic substrate **2a**, the one-pot protocol is not as effective for the conversion of **2e** into **4e**.

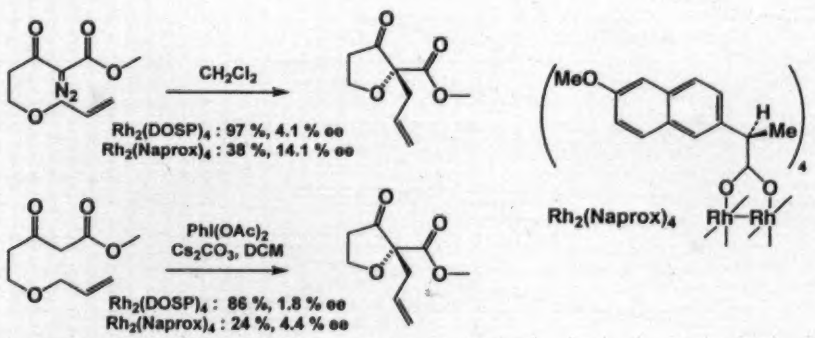


Scheme 3.4: The diazoketone- and iodonium ylide-mediated [2,3]-shift of an aromatic allyl ether substrate.

3.3.4. Asymmetric induction in the iodonium ylide-mediated [2,3]-shift.

It is known that chiral catalysts have been effective at inducing asymmetry in various carbenoid processes proceeding by iodonium ylides. We also attempted the asymmetric induction in the rearrangement of **2a** (Scheme 3.5). We chose to use the rhodium prolinato catalyst ($Rh_2(DOSP)_4$) as it has been found effective in various carbenoid mediated processes.[58] While this catalyst afforded the desired product in very

good yield (97 % from **3a**; 86 % from **2a**), it was weakly effective at inducing asymmetry (4.1 % ee from **3a**; 1.8 % ee from **2a**). We also attempted this reaction using rhodium naproxenate, $Rh_2(Naprox)_4$.[59] This was less effective at promoting the [2,3]-shift, affording **4a** in < 40 % yield for both protocols, but it did afford higher ee values (14.1 % from **3a**; 4.4 % from **2a**) than the $Rh_2(DOSP)_4$ catalyst. While the enantiomeric excesses afforded in these preliminary attempts were found to be small, they have provided evidence that asymmetric induction during the iodonium ylide mediated [2,3]-shift protocol is feasible.



Scheme 3.5: Asymmetric induction using chiral rhodium carboxylate catalysts.

3.4. Conclusions and Future Work

We have shown that the use of iodonium ylides as diazoketone surrogates for the generation and rearrangement of oxonium ylides is a feasible process. By optimizing the existing protocol for the formation of iodonium ylides, we were able to generate iodonium ylides in situ, in the presence of a transition metal catalyst. These ylides underwent carbene transfer with the catalyst to afford metallocarbenes, which underwent oxonium ylide formation and subsequent rearrangements.

This novel protocol was found to afford the products of the [2,3]-shift in 12 % and 23 % greater yield than the parent diazoketone mediated process. Though the [1,2]-shift

processes were found to be lower-yielding than the [2,3]-shifts, the product of the successful [1,2]-shift was isolated in 6 % greater yield than the parent diazoketone-mediated process. Regardless of protocol employed, the sulfonium ylide substrate intended to undergo the subsequent [1,2]-shift failed to do so. In all cases, even upon prolonged heating, the stable sulfonium ylide proved inert. The success of this diazoketone surrogate protocol in the aliphatic reaction series was not realized in the investigation of the aromatic series. The product of the [2,3]-shift was afforded in greater yield in all cases than it was from the iodonium ylide-mediated protocol.

We also demonstrated that asymmetric induction is possible for the iodonium ylide-mediated [2,3]-shift of a simple aliphatic substrate. Though the enantiomeric excesses observed were slight, these investigations have served to demonstrate the feasibility of this protocol.

Though this investigation was of a cursory nature, being limited to the use of di-stabilized diazoketone and iodonium ylide substrates, it has added to the knowledge concerning the use of iodonium ylides as diazo surrogates. Because chemoselectivity was not an issue in this investigation, further investigations could probe the efficacy of this protocol in processes required to form >5-membered onium ylides. Future investigations could also probe the synthesis of more complex bicyclic structures, on substrates having greater functional group density. It would also be worthwhile to determine whether or not the inefficiency of this new protocol in the rearrangement of aromatic substrates is an isolated incident or a broader issue.

To advance this protocol into the realm of general applicability, it would be necessary to develop a mild, chemoselective manner by which mono-stabilized iodonium ylides can be generated. Given the difficulty often encountered in diazoacylation reactions, the advent of such a procedure would be well received. This might entail the development of iodine reagents of greater electrophilicity, or the development of methods in which C-H acidities are increased in situ. There are numerous possibilities concerning

direction that this methodology might be taken, and it is expected that its use as a diazoketone surrogate in carbenoid reactions will continue to be expanded upon.

3.5. Experimental

3.5.1. General

Reactions were carried out in flame-dried glassware under a positive nitrogen atmosphere unless otherwise stated. Transfer of anhydrous solvents and reagents was accomplished with oven-dried syringes or cannula. Solvents were distilled before use: methylene chloride from calcium hydride, tetrahydrofuran and diethyl ether from sodium/benzophenone ketyl, toluene from sodium metal. Thin layer chromatography was performed on glass plates precoated with 0.25 mm Kieselgel 60 F_{254} (Merck). Flash chromatography columns were packed with 230-400 mesh silica gel (Merck). Radial chromatography was carried out on a Chromatotron 7924T (Harrison Research) with plates prepared using silica gel 60 F_{254} with gypsum binder (EM) on glass rotors.

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400 MHz or 500 MHz on Varian Inova 400 and 500, Mercury 400, or Unity 500 spectrometers, and the chemical shifts are reported on the δ scale (ppm) downfield from tetramethylsilane. Coupling constants (*J*) are reported in Hz. Second order splitting patterns are indicated by the J_{AB} notation. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; dd, doublet of doublets, etc. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 125 MHz and are reported (ppm) relative to the center line of a triplet at 77.23 ppm for deuterochloroform. Infrared (IR) spectra were measured with a Nicolet Magna 750 FT-IR infrared spectrophotometer. Mass spectra were determined on a Kratos Analytical MS-50 (EI) or Applied Biosystems Mariner Biospectrometry Workstation (ESI). Elemental analyses were obtained at the University of Alberta on a Carlo Erba CHNS-O EA 1108 Elemental Analyzer.

3.5.2. Substrate Syntheses

Bromomethyl Allyl Sulfide 1c. To a stirred solution of paraformaldehyde (8.0 g, 0.26 mol) in benzene (55 mL) was added 185 mL of 48 % HBr over a 5 minute period, and the reaction was stirred for 20 minutes at room temperature. The mixture was warmed to 40 °C and allyl mercaptan was added via addition funnel over 20 minutes. The mixture was then heated to 50 °C and stirred for an additional 2 hours. The benzene layer was then separated and washed successively with 50 mL of water and 50 mL of brine. The organic layer was then dried over magnesium sulfate and the benzene was removed by rotary evaporation. This was distilled (b.p. 53 °C, 11 mm Hg) to afford 5.4 g of the product as a clear, colourless liquid in 12 % yield: IR (CH_2Cl_2 cast) 3082, 3021, 2978, 2917, 1633, 1428, 1403, 1183, 990, 924 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.74 (dddd, J = 17.0, 9.8, 7.3, 7.3 Hz, 1H), 5.30 – 5.22 (m, 2H), 4.60 (s, 2H), 3.34 (d, J = 7.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.6, 119.2, 36.0, 34.3; HRMS (EI) calcd for C_4H_7SBr (M^+) 167.9431; found 167.9429.

Methyl 5-Allyloxy-3-oxopentanoate 2a. NaH (146 mg, 3.6 mmol, 1.1 eq) was added to a flame-dried 25 mL round bottom flask and rinsed with 10 mL of hexanes. The hexanes were removed, and to the flask was added 5.5 mL of THF. The flask was then gently evacuated and filled with argon to ensure an inert atmosphere. This was then cooled to 0 °C and methyl acetoacetate (375 μL, 3.5 mmol, 1.5 eq) was added dropwise. The resulting mixture stirred for 10 min.. To this was added *n*-BuLi (1.5 mL, 2.40M in hexanes, 1.1 eq) and the mixture was stirred for 10 minutes at 0 °C. Bromomethyl allylether **1a** (0.35 g, 2.3 mmol, 1 eq) was then added and the mixture was stirred for an additional 10 minutes. This was then quenched by the addition of 1 mL c.HCl / 5 mL water / 10 mL ether. The organic layer was separated and the aqueous layer was washed with two 10 mL portions of ether. The combined organic extracts were then washed with three 10 mL portions water, then 20 mL of brine. The organic layer was then dried over magnesium sulfate and concentrated by rotary evaporation. The product was purified by radial chromatography (2 mm plate, solvent ramp: 50 mL each of 2 %, 5 % then 15 % EtOAc / hexanes until the product was recovered) to afford 218 mg of **2a** as a clear oil in 51 % yield: R_f 0.45 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2955, 2869, 1748, 1718,

1437, 1314, 1145, 1101 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.86 (dddd, J = 17.3, 10.4, 5.6, 5.6 Hz, 1H), 5.24 (ddd, J = 17.3, 1.2, 1.2 Hz, 1H), 5.16 (ddd, J = 10.4, 1.2, 1.2 Hz, 1H), 3.95 (ddd, J = 5.5, 1.3, 1.3 Hz, 2H), 3.72 (s, 3H), 3.69 (t, J = 6.2 Hz, 2H), 3.50 (s, 2H), 2.79 (t, J = 6.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.2, 167.5, 134.4, 117.2, 72.1, 64.9, 52.3, 49.5, 43.1; HRMS (EI) calcd for $C_9H_{14}O_4$ (M^+) 186.0892; found 186.0890; Anal. Calcd for $C_9H_{14}O_4$: C, 58.05, H, 7.58. Found; C, 58.52, H, 7.58.

Methyl 5-Benzyloxy-3-oxopentanoate 2b. NaH (880 mg, 22.0 mmol, 1.15 eq) was added to a flame-dried 200 mL round bottom flask and rinsed with 15 mL of hexanes. The hexanes were removed and to the flask was added 55 mL of THF. The flask was then gently evacuated and filled with argon to ensure an inert atmosphere. This was then cooled to 0 °C and methyl acetoacetate (2.16 mL, 20 mmol, 1.05 eq) was added dropwise and the resulting orange mixture stirred for 10 min.. To this was added *n*BuLi (9.2 mL, 2.40M in hexanes, 1.15 eq) and the mixture was stirred for 10 minutes at 0 °C. Bromomethyl benzyl ether **1b** (3.82 g, 19 mmol, 1 eq) was then added and the mixture was stirred for an additional 10 minutes. This was then quenched by the addition of 4 mL of c.HCl / 20 mL of water / 30 mL of ether. The organic layer was separated and the aqueous layer washed with two 30 mL portions of ether. The combined organic extracts were then washed with three 30 mL portions water, then 30 mL of brine. The organic layer was then dried over magnesium sulfate and concentrated by rotary evaporation. The product was purified by gradient column chromatography (8 %, 15 % then 30 % EtOAc / hexanes until the product was recovered) to afford 2.66 g of **2b** as an oil in 59 % yield: R_f 0.44 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 3029, 2952, 2868, 1747, 1717, 1453, 1313, 1102 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.20 (m, 5H), 4.50 (s, 2H), 3.74 (t, J = 6.2 Hz, 2H), 3.71 (s, 3H), 3.49 (s, 2H), 2.82 (t, J = 6.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.2, 167.5, 137.9, 128.4, 127.7, 127.7, 73.3, 65.0, 52.3, 49.5, 43.2; HRMS (EI) calcd for $C_{13}H_{16}O_4$ (M^+) 236.1049; found 236.1041.

Methyl 5-Allylthio-3-oxopentanoate 2c. NaH (146 mg, 3.6 mmol, 1.1 eq) was added to a flame-dried 25 mL round bottom flask and rinsed with 10 mL of hexanes. The hexanes were removed, and to the flask was added 5.5 mL of THF. The flask was then gently

evacuated and filled with argon to ensure an inert atmosphere. This was then cooled to 0 °C and methyl acetoacetate (375 μL, 3.5 mmol, 1.5 eq) was added dropwise, and the resulting mixture was stirred for 10 min.. To this was added *n*-BuLi (1.5 mL, 2.40M in hexanes, 1.1 eq) and the mixture was stirred for 10 minutes at 0 °C. Bromomethyl allyl sulfide **1c** (0.387 g, 2.3 mmol, 1 eq) was then added and the mixture stirred for an additional 10 minutes. This was then quenched by the addition of 1 mL c.HCl / 5 mL of water / 10 mL of ether. The organic layer was separated and the aqueous layer washed with two 10 mL portions of ether. The combined organic extracts were then washed with three 10 mL portions water, then 20 mL of brine. The organic layer was then dried over magnesium sulfate and concentrated by rotary evaporation. The product was purified by gradient column chromatography (2 %, 4 %, 8 %, 15 %, then 30 % EtOAc / hexanes until the product was recovered) to afford 406 mg (60 %) of **2c** as a colourless oil: R_f 0.59 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2953, 1747, 1717, 1436, 1406, 1318, 1265 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.77 (dddd, J = 17.0, 9.9, 7.2, 7.2 Hz, 1H), 5.14 – 5.08 (m, 2H), 3.73 (s, 3H), 3.46 (s, 2H), 3.1 (d, J = 7.1 Hz, 2H), 2.82 (t, J = 7.1 Hz, 2H), 2.69 (t, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.8, 167.3, 134.1, 117.3, 52.4, 49.1, 42.9, 35.1, 24.2; HRMS (EI) calcd for $C_9H_{14}O_3S$ (M^+) 202.0664; found 202.0663.

Methyl 5-Benzylthio-3-oxopentanoate 2d. NaH (880 mg, 22.0 mmol, 1.15 eq) was added to a flame-dried 200 mL round bottom flask and rinsed with 15 mL of hexanes. The hexanes were removed and to the flask was added 55 mL of THF. The flask was then gently evacuated and filled with argon to ensure an inert atmosphere. This was then cooled to 0 °C and methyl acetoacetate (2.16 mL, 20 mmol, 1.05 eq) was added dropwise and the resulting orange mixture stirred for 10 min.. To this was added *n*BuLi (9.2 mL, 2.40M in hexanes, 1.15 eq) and the mixture was stirred for 10 minutes at 0 °C. Bromomethyl benzyl sulfide **1d** (4.13 g, 19 mmol, 1 eq) was then added and the mixture stirred for an additional 10 minutes. This was then quenched by the addition of 4 mL c.HCl / 20 mL water / 30 mL ether. The organic layer was separated and the aqueous layer washed with two 30 mL portions of ether. The combined organic extracts were then washed with three 30 mL portions water, then 30 mL of brine. The organic layer was then dried over magnesium sulfate and concentrated by rotary evaporation. The product

was purified by gradient column chromatography (2 %, 4 %, 8 %, 15 % then 30 % EtOAc / hexanes until the product was recovered) to afford 2.76 of **2d** as an oil in 58 % yield: R_f 0.56 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 3027, 2952, 1747, 1717, 1453, 1318 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (m, 4H), 7.20 (m, 1H), 3.72 (s, 3H), 3.71 (d, J = 1.9 Hz, 2H), 3.40 (s, 2H), 2.75 (t, J = 6.4 Hz, 2H), 2.66 (t, J = 6.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.8, 167.3, 138.1, 128.8, 128.6, 127.1, 52.4, 49.1, 42.8, 36.7, 24.9; HRMS (EI) calcd for $C_{13}H_{16}O_3S$ (M^+) 252.0820; found 252.0818.

Methyl 5-Allyloxy-2-dizao-3-oxopentanoate 3a. To a stirred solution of **2a** (458 mg, 2.46 mmol, 1 eq), Et_3N (343 mL, 2.46 mmol, 1 eq) in MeCN (5 mL) was added pTsN$_3$ (487 mg, 2.46 mmol, 1 eq) and the mixture was vigorously stirred at r.t. for 2.5 hours. The MeCN was then removed by rotary evaporation and the resulting oil dissolved in 30 mL ether. This was then washed with 5 mL of 25 % aq. KOH, 5 mL of 6 % aq. KOH then 10 mL water. The organic layer was then dried over sodium sulfate and concentrated by rotary evaporation. The product was purified by radial chromatography (4 mm plate, solvent ramp: 100 mL each of 2 %, 8 % then 30 % EtOAc / hexanes until the product was recovered) to afford 399 mg of **3a** as a pale yellow oil in 77 % yield: R_f 0.65 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2955, 2868, 2136, 1723, 1656, 1437, 1310, 1101 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.89 (dddd, J = 17.3, 10.4, 6.7, 6.7 Hz, 1H), 5.26 (ddd, J = 17.2, 1.6, 1.6 Hz, 1H), 5.17 (ddd, J = 10.3, 1.2, 1.2 Hz, 1H), 3.99 (ddd, J = 5.6, 1.4, 1.4 Hz, 2H), 3.83 (s, 3H), 3.77 (t, J = 6.3 Hz, 2H), 3.14 (t, J = 6.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.4, 161.7, 134.7, 117.0, 72.0, 64.9, 52.2, 40.3; HRMS (EI) calcd for $C_9H_{12}O_4N_2$ (M^+) 212.0797; found 212.0744.

Methyl 5-Benzyloxy-2-diazo-3-oxopentanoate 3b. To a stirred solution of **2b** (118 mg, 0.5 mmol, 1 eq), Et_3N (70 mL, 0.5 mmol, 1 eq) in MeCN (1 mL) was added pTsN$_3$ (99 mg, 0.5 mmol, 1 eq) and the mixture was vigorously stirred at r.t. for 2.5 hours. The MeCN was then removed by rotary evaporation and the resulting oil was dissolved in 10 mL ether. This was then washed with 2 mL of 25 % aq. KOH, 2 mL of 6 % aq. KOH, then 10 mL water. The organic layer was then dried over sodium sulfate and concentrated by rotary evaporation. The product was purified by radial chromatography (2 mm plate,

solvent ramp: 50 mL each of 2 %, 8 % then 30 % EtOAc / hexanes until the product was recovered) to afford 119 mg of **3b** as a pale yellow oil in 90 % yield: R_f 0.55 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2954, 2866, 2135, 1721, 1656, 1436, 1310, 1102 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.20 (m, 5H), 4.52 (s, 2H), 3.81 (s, 3H), 3.80 (t, J = 6.2 Hz, 2H), 3.17 (t, J = 6.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.4, 161.6, 138.2, 128.3, 127.7, 127.6, 73.1, 65.0, 52.2, 40.3; HRMS (EI) calcd for $C_{13}H_{14}O_4$ ($M-N_2^+$) 234.0892; found 234.0889.

Methyl 5-Allylthio-3-oxopentanoate 3c. To a stirred solution of **2c** (101 mg, 0.5 mmol, 1 eq), Et_3N (70 mL, 0.5 mmol, 1 eq) in MeCN (1 mL) was added pTsN$_3$ (99 mg, 0.5 mmol, 1 eq) and the mixture was vigorously stirred at r.t. for 2.5 hours. The MeCN was then removed by rotary evaporation and the resulting oil dissolved in 10 mL ether. This was then washed with 2 mL of 25 % aq. KOH, 2 mL of 6 % aq. KOH, then 10 mL water. The organic layer was then dried over sodium sulfate and concentrated by rotary evaporation. The product was purified by radial chromatography (2 mm plate, solvent ramp: 50 mL each of 2 %, 8 % then 30 % EtOAc / hexanes until the product was recovered) to afford 99 mg of **3c** as a pale yellow oil in 87 % yield: R_f 0.66 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2955, 2139, 1722, 1656, 1437, 1310, 1200 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.77 (dddd, J = 17.0, 9.9, 7.2, 7.2 Hz, 1H), 5.16 – 5.08 (m, 2H), 3.83 (s, 3H), 3.16 (br. d, 2H), 3.13 (d, J = 7.3 Hz, 2H), 2.77 (t, J = 7.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.8, 161.6, 134.2, 117.2, 52.2, 40.0, 34.9, 24.9; HRMS (EI) calcd for $C_9H_{12}O_3N_2S$ (M^+) 228.0569; found 228.0569.

Methyl 5-Benzylthio-3-oxopentanoate 3d. To a stirred solution of **2d** (126 mg, 0.5 mmol, 1 eq), Et_3N (70 mL, 0.5 mmol, 1 eq) in MeCN (1 mL) was added pTsN$_3$ (99 mg, 0.5 mmol, 1 eq) and the mixture was vigorously stirred at r.t. for 2.5 hours. The MeCN was then removed by rotary evaporation and the resulting oil dissolved in 10 mL ether. This was then washed with 2 mL of 25 % aq. KOH, 2 mL of 6 % aq. KOH, then 10 mL water. The organic layer was then dried over sodium sulfate and concentrated by rotary evaporation. The product was purified by radial chromatography (2 mm plate, solvent ramp: 50 mL each of 2 %, 8 % then 30 % EtOAc / hexanes until the product was

recovered) to afford 117 mg of **3d** as a pale yellow oil in 84 % yield: R_f 0.60 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 3061, 3027, 2953, 2139, 1721, 1656, 1436, 1364, 1310, 1202, 1126 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (m, 4H), 7.20 (m, 1H), 3.84 (s, 3H), 3.74 (s, 2H), 3.11 (t, J = 7.2 Hz, 2H), 2.72 (t, J = 7.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.7, 161.6, 138.2, 128.9, 128.5, 127.0, 52.2, 29.9, 36.6, 25.6; HRMS (EI) calcd for $C_{13}H_{14}O_3N_2S$ (M^+) 278.0725; found 278.0716.

Representative Rh-Catalyzed Diazo Decomposition Reaction: Conversion of 3a to 2-Allyl-2-carbomethoxytetrahydrofuran-3-one 4a. Into a stirred mixture of $Rh_2(OAc)_4$ (3 mg, 3 mol%) in CH_2Cl_2 (15 mL) at room temperature was added **3a** (50 mg, 0.24 mmol, 1 eq) in CH_2Cl_2 (9 mL) via cannula. The resulting reaction mixture was stirred for 10 minutes, at which time the reaction was found to be complete by T.L.C. analysis. The reaction mixture was then passed through a 2 cm plug of silica gel, eluting with ether. This was then concentrated to afford 38 mg of **4a** as a pale yellow oil 88 % yield: R_f 0.45 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2956, 2904, 1767, 17421238, 1148, 1113 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.70 (dddd, J = 17.5, 9.8, 7.3, 7.3 Hz, 1H), 5.18 – 5.19 (m, 2H), 4.39 – 4.29 (m, 2H), 3.77 (s, 3H), 2.75 (dddd, J = 14.3, 6.9, 1.2, 1.2 Hz, 1H), 2.56 (dddd, J = 14.3, 8.3, 1.2, 1.2 Hz, 1H), 2.60 – 2.51 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.5, 168.3, 130.8, 120.0, 85.6, 64.5, 52.9, 38.4, 36.2; HRMS (EI) calcd for $C_9H_{12}O_4$ (M^+) 184.0736; found 184.0735.

These conditions were also applied to **3b-e**.

Representative Cu-Catalyzed Diazo Decomposition Reaction: Conversion of 3c to 2-Allyl-2-carbomethoxytetrahydrothiophen-3-one 4c. Into a stirred mixture of $Cu(hfacac)_2$ (11 mg, 10 mol%) in CH_2Cl_2 (17 mL) at reflux was added **3c** (50 mg, 0.22 mmol, 1 eq) in CH_2Cl_2 (5 mL) via cannula. The resulting reaction mixture was stirred for 24 hours, at which time the reaction was found to be complete by T.L.C. analysis. The reaction was quenched by the addition of 15 mL of 0.5M K_2CO_3 and the bilayer separated. The aqueous layer was extracted with 15 mL CH_2Cl_2 and the combined organic extracts were washed with water (20 mL), bring (20 mL) then dried over

anhydrous magnesium sulfate and concentrated. The oil was then passed through a 2 cm plug of silica gel, eluting with ether. This was then concentrated to afford 39 mg of **4c** as a pale yellow oil in 89 % yield: R_f 0.64 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2953, 1747, 1733, 1232, 1129 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.80 (dddd, J = 17.8, 10.2, 7.7, 7.7 Hz, 1H), 5.16 – 5.10 (m, 2H), 3.74 (s, 3H), 3.16 (ddd, J = 16.4, 9.2, 7.2 Hz, 1H), 2.93 (ddd, J = 11.4, 8.5. 3.0 Hz, 1H), 2.87 (ddd, J = 17.9, 7.2, 3.0 Hz, 1H), 2.81 (dd, J = 14.5, 6.7 Hz, 1H), 2.69 (dd, J = 14.3, 7.7 Hz, 1H), 2.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.1, 170.8, 132.1, 119.8, 61.8, 52.9, 40.0, 37.4, 23.9; HRMS (EI) calcd for $C_9H_{12}O_3S$ (M^+) 200.0507; found 200.0509.

These conditions were also applied to **3a,b,d,e**.

Data for 2-Benzyl-2-carbomethoxytetrahydrofuran-3-one 4b: R_f 0.51 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 2954, 2903, 1767, 1743, 1496, 1261, 1233, 1138, 1119 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.18 (m, 5H), 4.24 (ddd, J = 9.2, 9.2, 7.3 Hz, 1H), 4.10 (ddd, J = 9.5, 9.5, 3.8 Hz, 1H), 3.75 (s, 3H), 3.24 (s, 2H), 2.44 (ddd, J = 18.2, 7.3, 3.7 Hz, 1H), 2.05 (ddd, J = 18.2, 9.4, 9.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.9, 168.5, 134.5, 130.6, 128.2, 127.0, 86.3, 64.6, 52.9, 40.0, 36.3; HRMS (EI) calcd for $C_{13}H_{14}O_4$ (M^+) 234.0892; found 234.0889; Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66, H, 6.02. Found, C, 66.41, H, 6.07.

Data for 2-Allyl-2-carboethoxy-3-oxo-2,3-dihydrobenzofuran 4e: R_f 0.45 (3:7 EtOAc / hexanes); IR (CH_2Cl_2 cast) 3080, 2984, 2938, 1750, 1726, 1612, 1478, 1463, 1300, 1249 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (m, 2H), 7.23 (d, J = 8.8 Hz, 1H), 7.12 (ddd, J = 7.1, 7.1, 0.8 Hz, 1H), 5.68 (dddd, J = 17.2, 10.2, 7.1, 7.1 Hz, 1H), 5.24 (m, J = 17.2 Hz, 1H), 5.10 (m, J = 10.2 Hz, 1H), 4.23 (m, 2H), 3.06 (dddd, J = 14.6, 7.1, 1.2, 1.1 Hz, 1H), 2.83 (dddd, J = 14.6, 7.1, 1.2, 1.1 Hz, 1H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.6, 172.3, 165.4, 138.5, 129.6, 124.9, 122.6, 120.7, 119.6, 113.5, 90.8, 62.6, 38.3, 14.0; HRMS (EI) calcd for $C_{14}H_{14}O_4$ (M^+) 246.0892; found 246.0883.

Copper-Catalyzed Diazo Decomposition of 3d: S-Benzyl Sulfonium Ylide 5. Into a stirred mixture of $Cu(hfacac)_2$ (8.3 mg, 10 mol%) in CH_2Cl_2 (12 mL) at reflux was added **3d** (47 mg, 0.17 mmol, 1 eq) in CH_2Cl_2 (5 mL) via cannula. The resulting reaction mixture was stirred for 14 hours, at which time **3d** was found to be consumed by T.L.C. analysis. The reaction mixture was quenched with 0.5M K_2CO_3 solution (15 mL) and the resulting layers separated. The aqueous layer was washed with CH_2Cl_2 (15 mL) and the resulting layers separated. The combined organic extracts were then washed with water (30 mL), pre-dried with brine (30 mL) and dried over anhydrous magnesium sulfate. This was then concentrated to give 32 mg of crude **5** as a white solid in 76 %. A sample of this was then recrystallized for characterization purposes from benzene / hexanes to give the purified product as colourless crystals: m.p.: 163-164 °C; IR (CH_2Cl_2 cast) 3028, 2989, 2943, 2846, 1685, 1577, 1432, 1366 1239 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.38 (m, 3H), 7.31 – 7.27 (m, 2H), 4.18 (d, J_{AB} = 13.1 Hz, 1H), 4.06 (d, J_{AB} = 13.1 Hz, 1H), 3.82 (s, 3H), 3.21 (ddd, J = 13.8, 10.6, 9.4 Hz, 1H), 2.98 (ddd, J = 13.6, 8.8, 1.4 Hz, 1H), 2.39 (ddd, J = 16.7, 9.2, 1.4 Hz, 1H), 2.03 (ddd, J = 16.6, 9.5, 8.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.0, 165.1, 130.3, 129.8, 129.5, 127.7, 51.6, 49.6, 34.4, 28.7 (signal for ylide carbon was not detected); HRMS (EI) calcd for $C_{13}H_{14}O_3S$ (M^+) 250.0664; found 250.0659; Anal. Calcd for $C_{13}H_{14}O_3S$: C, 62.38, H, 5.64, S, 12.81. Found, C, 62.25, H, 5.78, S, 13.25.

General Procedure for the One-Pot Iodonium Ylide Process. Into a stirred solution of the substrate in CH_2Cl_2 (0.05M) was added cesium carbonate (2.1 eq), bisacetoxyiodobenzene (1.1 eq) then the catalyst (3 mol% Rhodium, 10 mol% Copper). The reaction was then stirred until deemed complete by T.L.C. analysis. The reaction was then quenched by the addition of water and the bi-layer separated. The aqueous layer was extracted once with CH_2Cl_2 then the combined organic extracts were washed with water, then brine, dried over anhydrous magnesium sulfate and concentrated. The crude product was then purified by either gradient column chromatography or radial chromatography. The spectroscopic properties of all products obtained are identical to those formed in the diazoketone-mediated processes.

This procedure was applied to **2a-d** using $Rh_2(OAc)_4$ or $Cu(hfacac)_2$, and to **2e** using $Rh_2(OAc)_4$, $Rh_2(Piv)_4$, $Cu(hfacac)_2$ and $Cu(acac)_2$. The chiral catalysts $Rh_2(DOSP)_4$ and $Rh_2(Naprox)_4$ were also employed in this manner with substrate **2a**.

3.6. References

In Situ Generated Iodonium Ylides as Carbene Transfer Reagents

1. Aggarwal, V. K.; De Vicente, J.; Bonnert, R. V., Catalytic Cyclopropanation of Alkenes Using Diazo Compounds Generated in Situ. A Novel Route to 2-Arylcyclopropylamines. *Org. Lett.* **2001,** 3, (17), 2785-2788.

2. Aggarwal, V. K.; De Vicente, J.; Pelotier, B.; Holmes, I. P.; Bonnert, R. V., A Simple, User-Friendly Process for the Homologation of Aldehydes Using Tosylhydrazone Salts. *Tetrahedron Lett.* **2000,** 41, (52), 10327-10331.

3. Barrett, A. G. M.; Braddock, D. C.; Lenoir, I.; Tone, H., 5,10,15,20-Tetraphenylporphyrinato-Rhodium(III) Iodide Catalyzed Cyclopropanation Reactions of Alkenes Using Glycine Ester Hydrochloride. *J. Org. Chem.* **2001,** 66, (24), 8260-8263.

4. Dauban, P.; Saniere, L.; Tarrade, A.; Dodd, R. H., Copper-Catalyzed Nitrogen Transfer Mediated by Iodosylbenzene PhI=O. *J. Am. Chem. Soc.* **2001,** 123, (31), 7707-7708.

5. Müller, P.; Ghanem, A., Asymmetric Cyclopropanation of Olefins with an in Situ Generated Phenyliodonium Ylide. *Synlett* **2003**, (12), 1830-1833.

6. Wurz, R. P.; Charette, A. B., Hypervalent Iodine(III) Reagents as Safe Alternatives to Alpha-Nitro-Alpha-Diazocarbonyls. *Org. Lett.* **2003,** 5, (13), 2327-2329.

7. Wurz, R. P.; Charette, A. B., An Expedient and Practical Method for the Synthesis of a Diverse Series of Cyclopropane Alpha-Amino Acids and Amines. *J. Org. Chem.* **2004,** 69, (4), 1262-1269.

8. Dauban, P.; Dodd, R. H., Synthesis of Cyclic Sulfonamides Via Intramolecular Copper-Catalyzed Reaction of Unsaturated Iminoiodinanes. *Org. Lett.* **2000,** 2, (15), 2327-2329.

9. Espino, C. G.; Du Bois, J., A Rh-Catalyzed C-H Insertion Reaction for the Oxidative Conversion of Carbamates to Oxazolidinones. *Angewandte Chemie-International Edition* **2001,** 40, (3), 598-600.

10. Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J., Expanding the Scope of C-H Amination through Catalyst Design. *J. Am. Chem. Soc.* **2004,** 126, (47), 15378-15379.

11. Guthikonda, K.; Du Bois, J., A Unique and Highly Efficient Method for Catalytic Olefin Aziridination. *J. Am. Chem. Soc.* **2002,** 124, (46), 13672-13673.

12. Camacho, M. B.; Clark, A. E.; Liebrecht, T. A.; Deluca, J. P., A Phenyliodonium Ylide as a Precursor for Dicarboethoxycarbene: Demonstration of a Strategy for Carbene Generation. *J. Am. Chem. Soc.* **2000,** 122, (21), 5210-5211.

13. Müller, P.; Chappellet, S., Asymmetric 1,3-Dipolar Cycloadditions of 2-Diazocyclohexane-1,3-Diones and Alkyl Diazopyruvates. *Helv. Chim. Acta* **2005,** 88, (5), 1010-1021.

14. Dess, D. B.; Martin, J. C., A Useful 12-I-5 Triacetoxyperiodinane (the Dess-Martin Periodinane) for the Selective Oxidation of Primary or Secondary Alcohols and a Variety of Related 12-I-5 Species. *J. Am. Chem. Soc.* **1991,** 113, (19), 7277-7287.

15. Nicolaou, K. C.; Baran, P. S.; Zhong, Y. L., Selective Oxidation at Carbon Adjacent to Aromatic Systems with Ibx. *J. Am. Chem. Soc.* **2001,** 123, (13), 3183-3185.

16. Nicolaou, K. C.; Baran, P. S.; Zhong, Y. L.; Barluenga, S.; Hunt, K. W.; Kranich, R.; Vega, J. A., Iodine(V) Reagents in Organic Synthesis. Part 3. New Routes to Heterocyclic Compounds Via O-Iodoxybenzoic Acid-Mediated Cyclizations: Generality, Scope, and Mechanism. *J. Am. Chem. Soc.* **2002,** 124, (10), 2233-2244.

17. Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T., O-Iodoxybenzoic Acid (Ibx) as a Viable Reagent in the Manipulation of Nitrogen- and Sulfur-Containing Substrates: Scope, Generality, and Mechanism of Ibx-Mediated Amine Oxidations and Dithiane Deprotections. *J. Am. Chem. Soc.* **2004,** 126, (16), 5192-5201.

18. Tamura, Y.; Yakura, T.; Tohma, H.; Kikuchi, K.; Kita, Y., Hypervalent Iodine Oxidation of Para-Alkoxy-Phenol and Related Phenol - a Facile and Efficient Synthesis of Para-Quinones. *Synthesis-Stuttgart* **1989**, (2), 126-127.

19. Karam, O.; Jacquesy, J. C.; Jouannetaud, M. P., Nucleophilic Para-Fluorination of 4-Alkylphenols by Hypervalent Iodine Reagent and Pyridinium Polyhydrogen Fluoride (Pphf) a Novel Route to 4-Fluorocyclohexa-2,5-Dienones. *Tetrahedron Lett.* **1994,** 35, (16), 2541-2544.

20. Kita, Y.; Egi, M.; Takada, T.; Tohma, H., Development of Novel Reactions Using Hypervalent Iodine(III) Reagents: Total Synthesis of Sulfur-Containing Pyrroloiminoquinone Marine Product, (+/-)-Makaluvamine F. *Synthesis-Stuttgart* **1999**, (5), 885-897.

21. Mitchell, A. S.; Russell, R. A., Oxidations of Substituted Phenols with Hypervalent Iodine - Applications to the Phthalide Annulation Route to Anthraquinones. *Tetrahedron Lett.* **1993**, 34, (3), 545-548.

22. Moriarty, R. M.; Berglund, B. A.; Penmasta, R., Direct Alpha-Hydroxylation of Ketones under Acidic Conditions Using [Bis (Trifluoroacetoxy)] Iodobenzene. *Tetrahedron Lett.* **1992**, 33, (41), 6065-6068.

23. Moriarty, R. M.; Prakash, O., Hypervalent Iodine in Organic-Synthesis. *Acc. Chem. Res.* **1986**, 19, (8), 244-250.

24. Tamura, Y.; Yakura, T.; Shirouchi, Y.; Haruta, J. I., Pummerer-Type Reaction of Alpha-Acylsulfides Using Phenyl Iodosyl Bis(Trifluoroacetate). *Chem. Pharm. Bull.* **1986**, 34, (3), 1061-1066.

25. Moriarty, R. M., Organohypervalent Iodine: Development, Applications, and Future Directions. *J. Org. Chem.* **2005**, 70, (8), 2893-2903.

26. Schank, K.; Lick, C., Ozonolytic Fragmentation of Phenyliodonium Beta-Diketonates - a Convenient Synthesis of Unsolvated Vic-Triketones. *Synthesis-Stuttgart* **1983**, (5), 392-395.

27. Gudrinieste, E.; Neiland, O.; Vanag, G., *Zh. Obsch. Khim.* **1957**, 27, 2737.

28. Hayasi, Y.; Okada, T.; Kawanisi, M., Cyclic Diacylcarbene Generated from Iodonium Ylides and Diazodiketones. *Bull. Chem. Soc. Jpn.* **1970**, 43, (8), 2506.

29. Hadjiarapoglou, L.; Spyroudis, S.; Varvoglis, A., Phenyliodonium Bis(Phenylsulfonyl)Methylide - a New Hypervalent Iodonium Ylide. *J. Am. Chem. Soc.* **1985,** 107, (24), 7178-7179.

30. Hood, J. N. C.; Lloyd, D.; Macdonald, W. A.; Shepherd, T. M., The Effect of Different Copper (and Some Other) Catalysts on the Conversion of Triphenyl- and Some Tetraphenyl-Diazocyclopentadienes and of Some Phenyliodonium α,α'-Diazocarbonylylides into Arsonium or Other Ylides. *Tetrahedron* **1982,** 38, 3355-3358.

31. Zhdankin, V. V., A Tribute - Professor Anastasios Varvoglis. *Arkivoc* **2003**, 1-10.

32. Müller, P., Asymmetric Transfer of Carbenes with Phenyliodonium Ylides. *Acc. Chem. Res.* **2004,** 37, (4), 243-251.

33. Müller, P.; Ghanem, A., Rh(II)-Catalyzed Enantioselective Cyclopropanation of Olefins with Dimethyl Malonate Via in Situ Generated Phenyliodonium Ylide. *Org. Lett.* **2004,** 6, (23), 4347-4350.

34. Eberlein, T. H.; West, F. G.; Tester, R. W., The Stevens [1,2]-Shift of Oxonium Ylides - a Route to Substituted Tetrahydrofuranones. *J. Org. Chem.* **1992,** 57, (12), 3479-3482.

35. Marmsäter, F. P.; Murphy, G. K.; West, F. G., Cyclooctanoid Ring Systems from Mixed Acetals Via Heteroatom-Assisted [1,2]-Shift of Oxonium Ylides. *J. Am. Chem. Soc.* **2003,** 125, (48), 14724-14725.

36. Marmsäter, F. P.; West, F. G., Iterative Approach to Polycyclic Ethers Based on Stereoselective Oxonium Ylide [2,3]-Shifts. *J. Am. Chem. Soc.* **2001,** 123, (21), 5144-5145.

37. Murphy, G. K.; West, F. G., Hydrazulene Ring Systems Via Heteroatom-Assisted [1,2]-Shift of Oxonium and Sulfonium Ylides. *Org. Lett.* **2005,** 7, (9), 1801-1804.

38. Tester, R. W.; West, F. G., Medium Ring Ethers Via [1,2]-Shift of Acetal-Derived Oxonium Ylides. *Tetrahedron Lett.* **1998,** 39, (26), 4631-4634.

39. Ochiai, M.; Kitagawa, Y., Reaction of Lambda(3)-Vinyhodanes: Generation and Alkylidene-Transfer of Monocarbonyl Iodonium Ylides. *J. Syn. Org. Chem. Jpn.* **2000,** 58, (11), 1048-1056.

40. Ochiai, M.; Kitagawa, Y.; Yamamoto, S., Generation and Reaction of Monocarbonyliodonium Ylides: Ester Exchange of (Z)-(Beta-Acetoxyvinyl)Iodonium Salts with Lithium Ethoxide and Synthesis of Alpha,Beta-Epoxy Ketones. *J. Am. Chem. Soc.* **1997,** 119, (48), 11598-11604.

41. Huckin, S. N.; Weiler, L., Alkylation of Dianions of Beta-Keto-Esters. *J. Am. Chem. Soc.* **1974,** 96, (4), 1082-1087.

42. Kawasaki, T.; Kimachi, T., Sparteine-Mediated Enantioselective [2,3]-Wittig Rearrangement of Allyl Ortho-Substituted Benzyl Ethers and Ortho-Substituted Benzyl Prenyl Ethers. *Tetrahedron* **1999,** 55, (22), 6847-6862.

43. Reich, H. J.; Jasperse, C. P.; Renga, J. M., Organoselenium Chemistry - Alkylation of Acid, Ester, Amide, and Ketone Enolates with Bromomethyl Benzyl Selenide and Sulfide - Preparation of Selenocysteine Derivatives. *J. Org. Chem.* **1986,** 51, (15), 2981-2988.

44. Regitz, M., Transfer of Diazo Groups. *Angew. Chem., Int. Ed.* **1967,** 6, (9), 733.

45. West, F. G.; Naidu, B. N.; Tester, R. W., Profound Catalyst Effects in the Generation and Reactivity of Carbenoid-Derived Cyclic Ylides. *J. Org. Chem.* **1994,** 59, (23), 6892-6894.

46. Marmsäter, F. P.; Vanecko, J. A.; West, F. G., Cyclic Oxonium Ylides: Building Blocks for Iterative Synthesis of Polycyclic Ethers. *Tetrahedron* **2002,** 58, (10), 2027-2040.

47. Marmsäter, F. P.; Vanecko, J. A.; West, F. G., Catalyst and Ring Size Effects on Periselectivity of Oxonium Ylide Rearrangements. *Org. Lett.* **2004,** 6, (10), 1657-1660.

48. Cheng, J. P.; Liu, B.; Zhao, Y. Y.; Sun, Y. K.; Zhang, X. M.; Lu, Y., Effects of Adjacent Onium Cations and Remote Substituents on the H-A(+) Bond Equilibrium Acidities in Dimethyl Sulfoxide Solution. An Extensive Ylide Thermodynamic Stability Scale and Implication for the Importance of Resonance Effect on Ylide Stabilities. *J. Org. Chem.* **1999,** 64, (2), 604-610.

49. Clark, J. S., Nitrogen, Oxygen and Sulfur Ylide Chemistry. A Practical Approach in Chemistry. **2002,** (11), 297.

50. Felthouse, T. R., The Chemistry, Structure, and Metal Metal-Bonding in Compounds of Rhodium(II). *Prog. Inorg. Chem.* **1982,** 29, 73-166.

51. Moody, C. J.; Taylor, R. J., Rhodium Carbenoid Mediated Cyclizations .5. Synthesis and Rearrangement of Cyclic Sulfonium Ylides - Preparation of 6-Membered and 7-Membered Sulfur Heterocycles. *Tetrahedron* **1990,** 46, (18), 6501-6524.

52. Prakash, O.; Sharma, V.; Tanwar, M. P., Hypervalent Iodine Oxidation of Alpha-Substituted 2,4-Dihydroxyacetophenones: Synthesis of Novel O-Iodophenoxy Ethers Via Rearrangement of Iodonium Ylides. *Can. J. Chem.* **1999,** 77, (7), 1191-1195.

53. Pohnert, G., Phenyliodine(III) Bis(Trifluoroacetate) (PIFA). *Journal Fur Praktische Chemie-Practical Applications and Applied Chemistry* **2000,** 342, (7), 731-734.

54. Doyle, M. P.; Forbes, D. C., Recent Advances in Asymmetric Catalytic Metal Carbene Transformations. *Chem. Rev.* **1998,** 98, (2), 911-935.

55. Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B., Stereoselective Cyclopropanation Reactions. *Chem. Rev.* **2003,** 103, (4), 977-1050.

56. Salomon, R. G.; Kochi, J. K., Copper(I) Catalysis in Cyclopropanations with Diazo-Compounds - Role of Olefin Coordination. *J. Am. Chem. Soc.* **1973,** 95, (10), 3300-3310.

57. Pirrung, M. C.; Werner, J. A., Intramolecular Generation and [2,3]-Sigmatropic Rearrangement of Oxonium Ylides. *J. Am. Chem. Soc.* **1986,** 108, (19), 6060-6062.

58. Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J., Asymmetric Cyclopropanations by Rhodium(II) N-(Arylsulfonyl)Prolinate Catalyzed Decomposition of Vinyldiazomethanes in the Presence of Alkenes. Practical Enantioselective Synthesis of the Four Stereoisomers of 2-Phenylcyclopropan-1-Amino Acid. *J. Am. Chem. Soc.* **1996,** 118, (29), 6897-6907.

59. Liu, X.; West, F. G. University of Alberta, Edmonton, 2004.

4. Chapter 4

In Situ Generated Iodonium Ylides as Carbene Transfer Reagents

4.1. Introduction

The natural product dactylol is an irregular isoprenoid isolated from a marine organism. The structure of dactylol is a *trans*-fused, 5-8 bicyclic skeleton with bridgehead oxygenation. Though this molecule has little to no known biological activity, it has been the objective of a number of total syntheses. The simple nature of the carbocyclic framework has made dactylol a useful proving ground for methodologies in the synthesis of medium-sized rings. A total of six research groups have published total syntheses of this molecule, employing ring-expansion, cycloaddition, annulation and ring-closing metathesis protocols. We have also investigated the total synthesis of (+)-dactylol employing our heteroatom-stabilized Stevens [1,2]-shift of mixed thioacetal-derived oxonium ylide protocol. Our efforts toward the synthesis of this natural product will be discussed in this chapter.

4.2. Background

4.2.1. Biosynthesis

The natural product (+)-dactylol (**1**) is an irregular isoperenoid isolated from the Caribbean sea hare *Aplysia dactylomela*,[1] and its putative food source *Laurencia poitei*.[2] This isoprenoid is believed to be biosynthetically derived from humulene (**2**),[3-6] and is

therefore one of a number of related molecules including poitediol[2] (**3**), precapnelladiene (**4**) and africanol (**5**) (Figure 4.1). These isoprenoids are all similar, having a medium-sized ring fused to a smaller 5-membered ring.

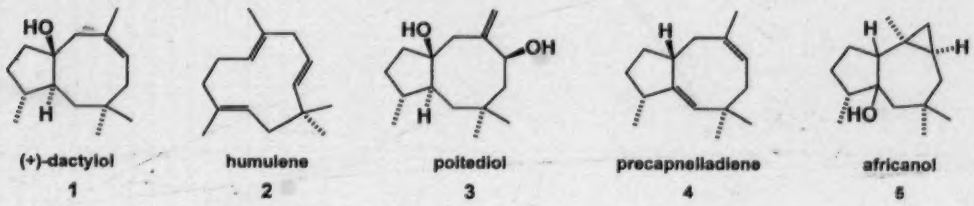


Figure 4.1: Structures of natural products biosynthetically-derived from humulene **2**.

The irregular structure of dactylol is believed to be a result of the "cyclopropane sliding" reaction in which a 7-membered ring is expanded to an eight membered ring during its biosynthesis (Figure 4.2). It is believed that dactylol is derived from humulene (**2**), intercepting the 6-africyl cation (**8**) along the biosynthetic pathway of africanol, **5**.[6] The "cyclopropane sliding" reaction is believed to occur by the cyclopropane shifting to stabilize the cationic charge of the 6-africyl cation (**7**), giving cation **9**, which affords dactylol upon hydrolysis.

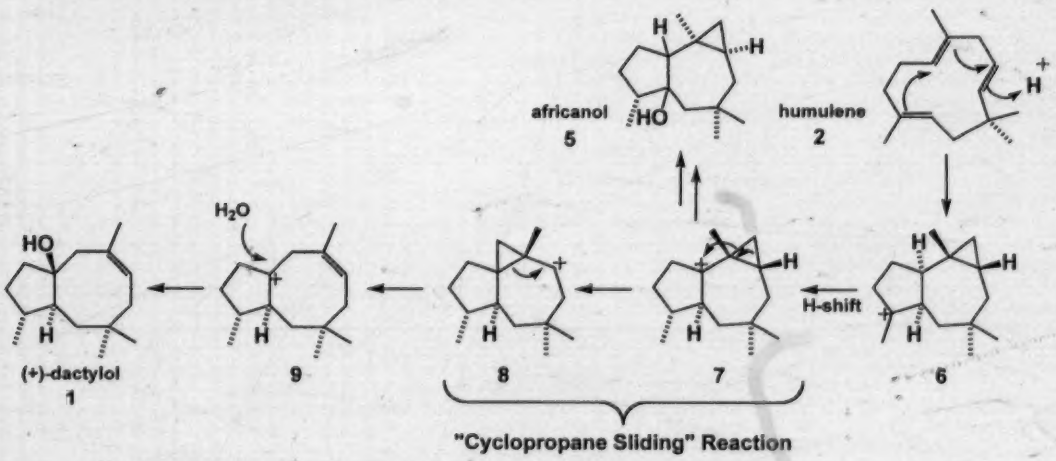
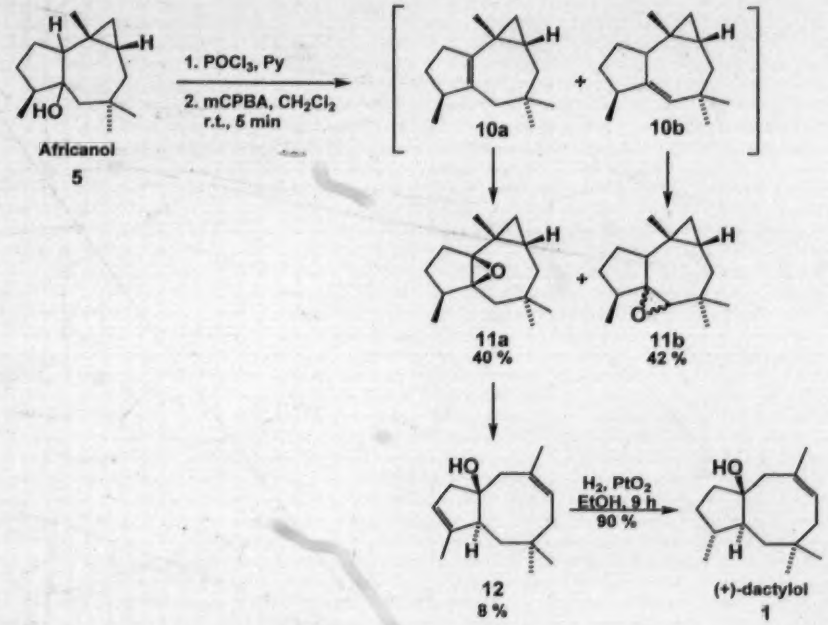


Figure 4.2: Proposed mechanism of the biosynthesis of (+)-dactylol from humulene.

Though dactylol has little to no known biological activity, it has been synthesized on many occasions. Dactylol has a *trans*-fused 5-8 bicyclic skeleton with a bridgehead alcohol, and the attention afforded this isoprenoid is a result of its simple, yet synthetically challenging structure. As a result, dactylol became a frequent proving ground for those developing new methods for the synthesis of fused, bicyclic systems containing medium sized rings.

4.2.2. The Hayasaka Synthesis of Dactylol

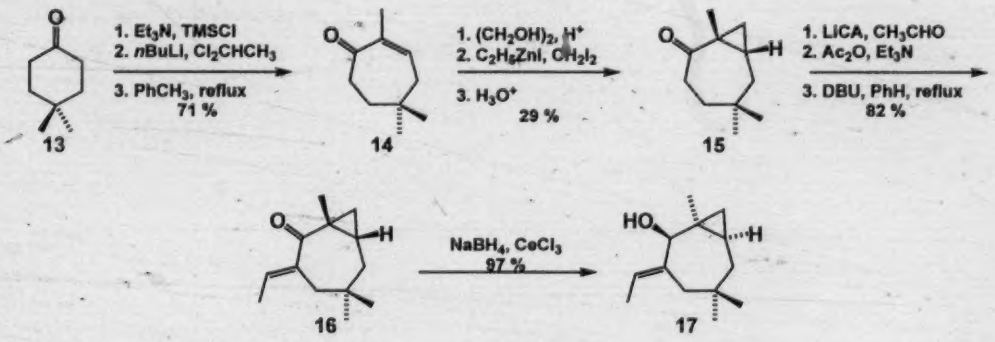
The original racemic synthesis of dactylol by Haysaka and co-workers probed the proposed biosynthetic pathway.[3] Believing it to be derived from humulene **2**, as a derivative of the africyl cation **7**, africanol was chosen as the starting material. Africanol **5** was treated with $POCl_3$ and pyridine to effect a dehydration, and the subsequent mixture of alkenes **10a,b** was epoxidized with *m*CPBA, affording **11a,b** in 82 % yield (Scheme 4.1). Upon treatment of **11a** with $BF_3 \bullet OEt_2$, the substrate underwent the "cyclopropane sliding" rearrangement, expanding to the cyclooctanoid **12** in 8 % yield. Subsequent hydrogenation of this with Adams[7-9] catalyst afforded dactylol, **1**.



Scheme 4.1: The synthesis of dactylol **1** from africanol **5**.

4.2.3. The Paquette Synthesis of Dactylol

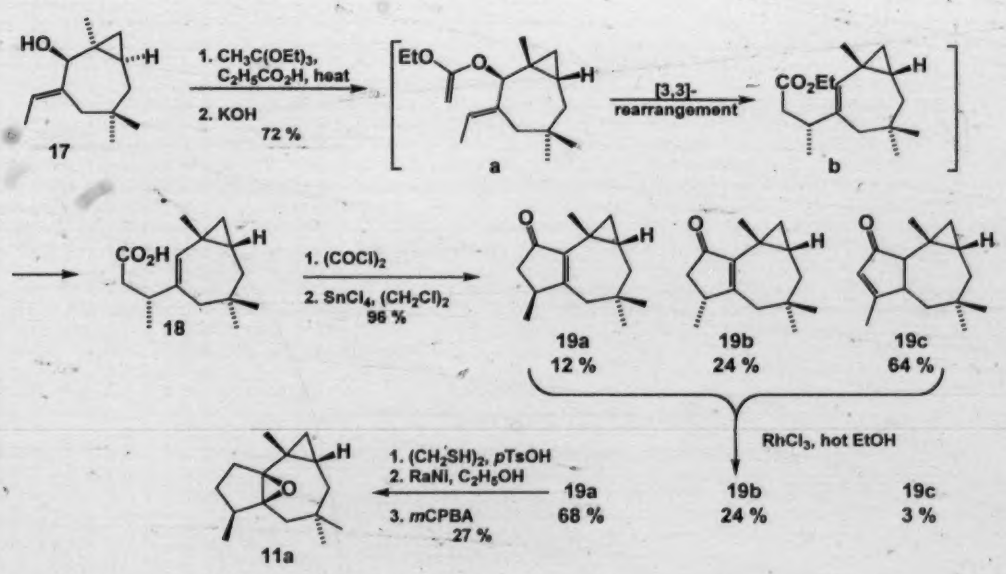
Paquette and co-workers undertook the second synthesis of dactylol, a formal synthesis intercepting the Hayasaka intermediate **11a**. They constructed this by using a combination of the Saegusa[10,11] ring expansion and the ortho ester Claisen rearrangement. The synthesis started with 4,4-dimethylcyclohexanone **13**, which was trapped as the trimethylsilyl enol ether, and then cyclopropanated with chloromethyl carbene (Scheme 4.2).[12] Heating of this in toluene afforded the ring-expanded cycloheptenone **14**. The ketone was protected, and the olefin cyclopropanated under standard conditions to give **15** upon hydrolysis of the ketal.[13] An exocyclic ethylidene group was stereoselectively introduced by treating the enolate of **15** with acetaldehyde, then eliminating the subsequent acetate with DBU in benzene, to give **16** in 82 % yield. A stereoselective Luche[14] reduction of carbonyl **16** gave alcohol **17**.



Scheme 4.2: The Paquette synthesis of dactylol, part 1.

Alcohol **17** was treated with triethyl orthoformate in ethanol to give intermediate **a** (Scheme 4.3). Heating enabled the [3,3]-rearrangement to afford **b**, which was saponified to give acid **18**. Conversion of this to the acid chloride, and treating with stannic chloride gave a mixture of bicyclic alkenes **19a**, **19b** and **19c**. The desired **19a** consisted of only 12 % of the product mixture, but the authors found that treating the mixture with rhodium (III) chloride in hot ethanol effected an isomerization in which **19c**

was mostly converted into **19a**.[15] The ketone of **19a** was removed by a tandem dithiolane formation / RaNi reduction sequence. Treatment of this with *m*CPBA afforded the Hayasaka intermediate **11a** in 27 % yield over the final three steps. This intermediate was shown to afford dactylol in low yield upon treatment with Lewis acid, followed by hydrogenation.[3]

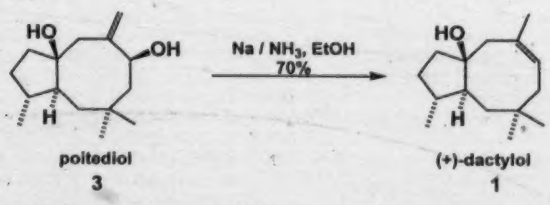


Scheme 4.3: The Paquette synthesis of dactylol, part 2.

4.2.4. The Gadwood Syntheses of Dactylol

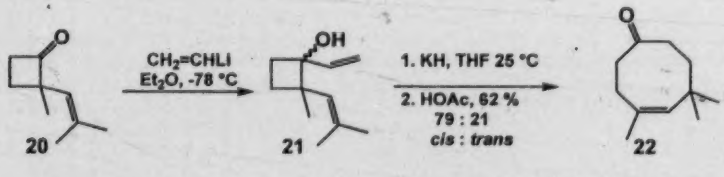
Both of the early dactylol syntheses were based on the proposed biosynthetic pathway involving the isomerization of a suitable cycloheptane precursor, in low yield. The first dactylol synthesis by Gadwood and co-workers[16] involved a one-step process, reductively rearranging the similar natural product poitediol, **3**. Given the knowledge concerning the reductive rearrangement of allyl alcohols, the authors believed dactylol to be available from poitediol **3** by a standard Birch[17,18] reduction. In the event **3** was

treated with sodium metal in a liquid ammonia / ethanol mixture to afford dactylol in 70 % yield (Scheme 4.4).



Scheme 4.4: Gadwood synthesis of (+)-dactylol **1** from poitediol **3.**

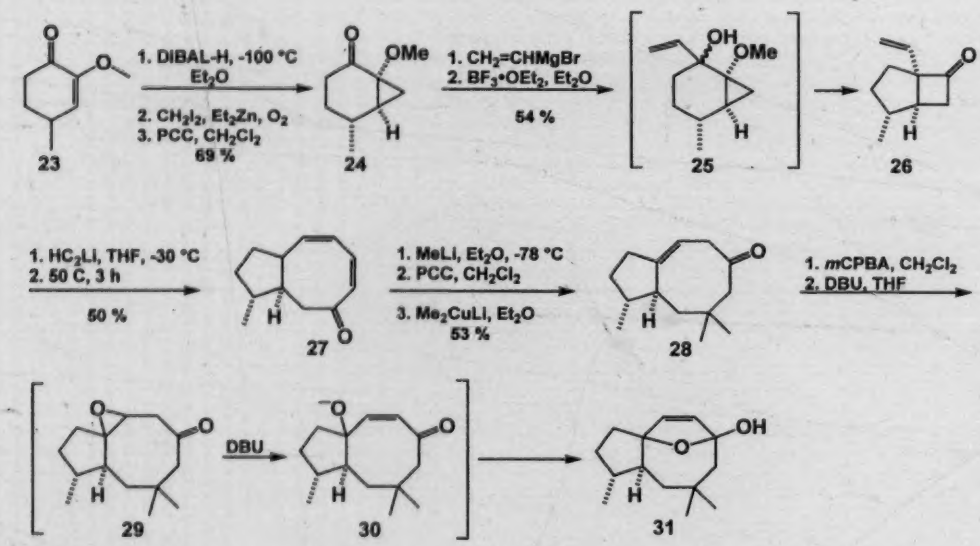
Because dactylol was shown to be available in few steps from other similar natural products, and given its lack of reported biological activity, it may have seemed that further synthetic efforts were unnecessary. The continuing synthetic attraction of dactylol is measured by its synthesis being subsequently attempted by no less than seven different strategies. As suggested earlier, dactylol became a common proving ground for those wishing to apply mew methods for preparing fused, medium-sized rings in a total synthesis. The first to do so were again Gadwood and co-workers. They had investigated the anionic oxy Cope rearrangement of divinyl cyclobutanols, and demonstrated that this protocol readily afforded cyclooctanones in good yield and with good stereoselectivity (Scheme 4.5).[19]



Scheme 4.5: Representative example of the divinyl cyclobutanol anionic oxy-Cope rearrangement from Gadwood.

As part of their program directed toward the synthesis of cyclooctanoid natural products, they employed this protocol in the synthesis of dactylol.[20] Cyclohexenone **23**

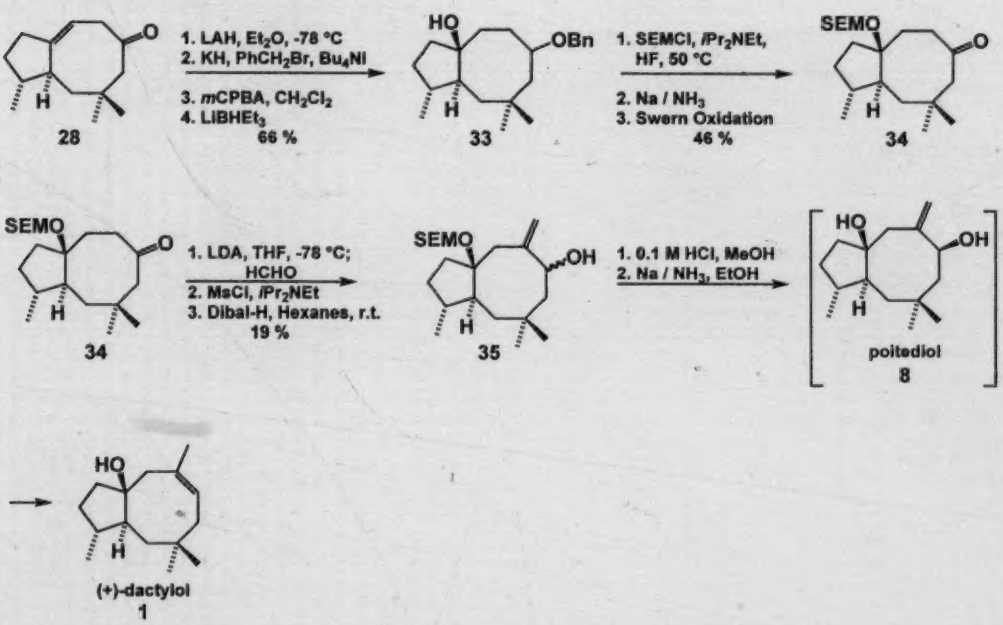
was converted to bicycle **24** by a reduction / cyclopropanation / oxidation sequence in 69 % yield (Scheme 4.6). Treatment of **24** with vinylmagnesium bromide, followed by a Lewis acid mediated ring expansion[21,22] of **25** gave cyclobutanone **26** in 54 % yield. Cyclobutanone **26** was treated with lithium acetylide, and then heated for 3 hours to afford the allenolate product of the [3,3]-rearrangement, which gave **27** in 50 % yield upon workup. Having shown this to undergo the desired rearrangement, giving the required ring fused bicycle with the necessary stereochemical centres, they continued on with the total synthesis. The geminal dimethyl groups were installed by a methylation / oxidation with allylic transposition / conjugate methyl addition sequence, which gave **28** in 53% yield. Alkene **28** underwent epoxidation with *m*-CPBA (giving **29**), which was treated with base to cleave the epoxide by β-elimination and install the necessary bridgehead alcohol of **30**. However, upon opening the epoxide, the alkoxide **30** underwent a transannular hemi-ketalizaion to give **31**, which the authors found to be synthetically unworkable.



Scheme 4.6: The second Gadwood synthesis of dactylol, part 1.

To complete the synthesis, the authors devised an alternate endgame. Ketone **28** was reduced to the corresponding alcohol, and protected as the benzyl ether (Scheme

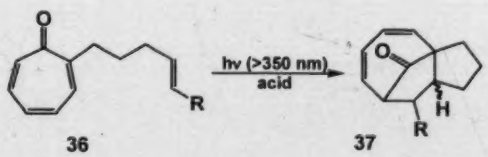
4.7). Treatment with *m*-CPBA gave the epoxide, which was cleaved with $LiBHEt_3$ to give **33**, with the necessary bridgehead alcohol. This alcohol was protected as the [(trimethylsilyl)ethoxy]methyl ether, so as to prevent hemi-ketalization from occurring after cleavage of the benzyl ether and Swern oxidation (which gave **34**). The exo-methylene group required for the synthesis of poitediol was installed by a formaldehyde-mediated exo-olefination followed by elimination of the resulting mesylated alcohol. Reduction of the carbonyl gave **35**, which afforded poitediol **3** upon removal of the SEM protecting group. Poitediol was then converted into dactylol **1** by a dissolving metal reduction. While the anionic oxy-Cope protocol was effective in preparing the fused bicyclic cyclooctanoid, the latter conversion of this intermediate into dactylol suffered from a transannular hemi-ketalizaion. This necessitated the incorporation of numerous additional steps to complete the synthesis.



Scheme 4.7: The second Gadwood synthesis of dactylol, part 1.

4.2.5. The Feldman Synthesis of (+)-Dactylol

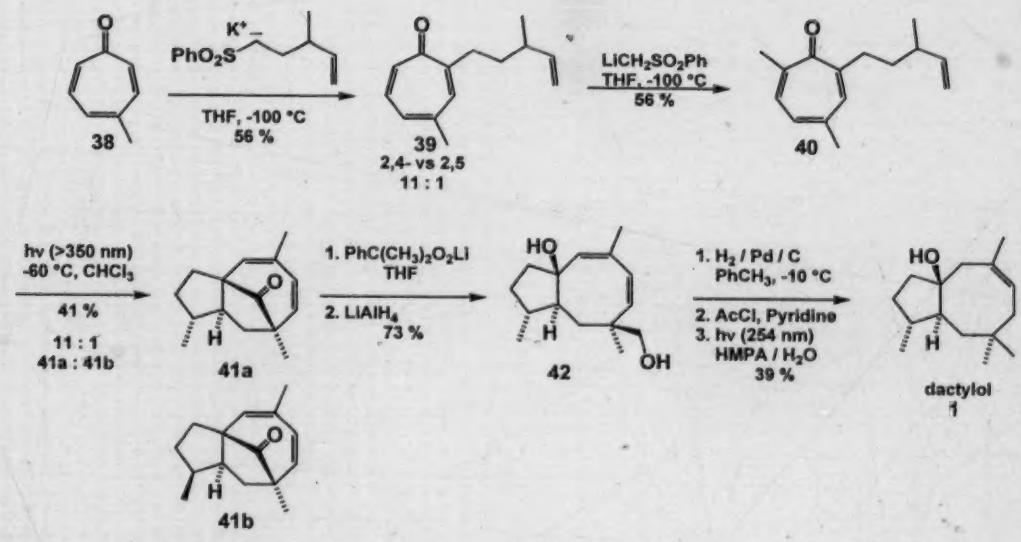
The next synthesis of dactylol to appear in the literature was from Feldman and co-workers. Having previously disclosed several examples of the tropone-alkene [6π + 2π] photocycloaddition, such as **36** to **37**, (Scheme 4.8), the authors believed this method to be a complement to existing methods for the synthesis of the bicyclo[6.3.0]undecane skeleton.[23-25] As an application of this methodology, they undertook the total synthesis of dactylol.[26, 27]



36 37

Scheme 4.8: Representative example of the tropone-alkene [6π+2π] photocycloaddition.

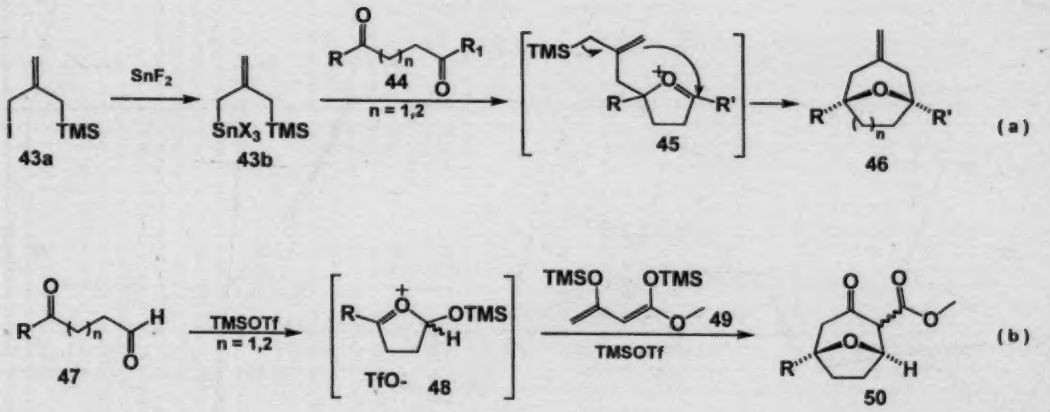
The photocycloaddition precursor **40** was prepared by a dialkylation of 4-methyltropone **38** using Funk's alkylation chemistry (Scheme 4.9).[28] Irradiation of **40** at low temperature afforded an 11 : 1 ratio of **41a** and **41b**, favoring the desired product. Treatment of **41a** under numerous conditions known to effect the Baeyer-Villiger reaction was found to be ineffective. The authors eventually found the Corey protocol[29] to be effective, affording the desired lactone, which was immediately reduced with lithium aluminum hydride to give diol **42** in 73 % yield. Hydrogenation of diene **42** afforded the desired tri-substituted olefin. Next, the primary alcohol was converted to the corresponding acetate, and then reduced by photo-reductive deacetylization[30] upon photolysis with 254 nm light to give dactylol in 39 % yield. This represented a concise and stereoselective racemic synthesis of dactylol. The authors effectively demonstrated the use of the tropone-alkene photocycloaddition in this synthesis, constructing the cyclooctanoid in a single step with substrate-controlled induction of relative asymmetry.



Scheme 4.9: The Feldman synthesis of dactylol.

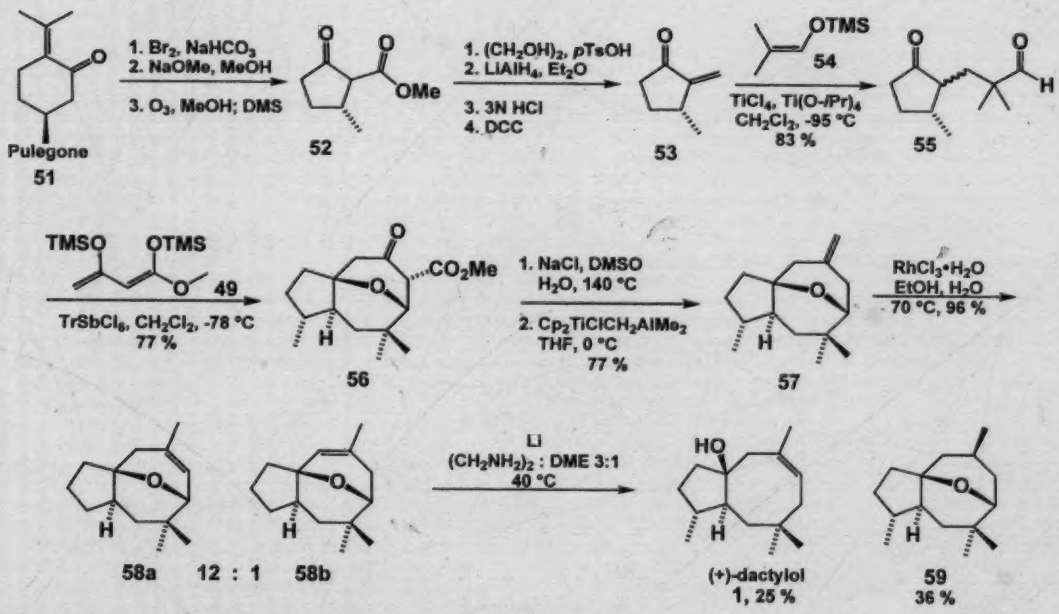
4.2.6. The Molander Synthesis of (+)-Dactylol

The Molander synthesis of dactylol was the first asymmetric synthesis of the natural product. Furthermore, this was also the first use of a natural product-derived small molecule to stereospecifically install the methyl group on the 5-membered ring.[31] Molander and co-workers initially published a novel approach to 7- and 8-membered rings by either a [3+4] or [3+5] annulation protocol. The first-generation of this methodology involved the preparation of a dinucleophilic synthon **43**, and treating this with a 1,4 or 1,5 dicarbonyl electrophile **44** and a Lewis acid to give **46** via the oxocarbenium ion **45** (Scheme 4.10, eq. a).[32, 33] This method was further developed into a more general strategy by treating the bis-silyl enol ether of methylacetoacetate **49** and a 1,4- or 1,5-keto aldehyde **47** with a Lewis acid (Scheme 4.10, eq. b).[34-37] This methodology was shown to afford products **50** in high diastereomeric ratios, often as single regioisomers from intermediate **48**. The annulation product from the second-generation synthesis is functionalized with a carbonyl and a carbomethoxy group, which might facilitate subsequent transformations on the medium-sized ring.



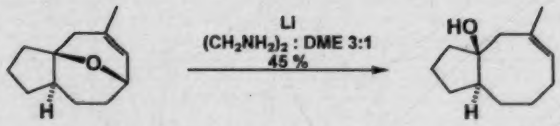
Scheme 4.10: The annulation protocol developed by Molander for the synthesis medium-sized rings.

The Molander synthesis of dactylol employed the enone **53**, which was derived from **52**, which in turn comes from the natural product (+)-pulegone **51**.[38] The starting material **52** can easily be prepared in gram quantities, and as a result, it has since been employed in two additional approaches to (+)-dactylol. Methyl pulegonate **52** was protected as the ketal, the ester was reduced to the primary alcohol and the ketal was removed (Scheme 4.11). A DCC-mediated dehydration of this alcohol afforded **53**. Treatment of **53** with the trimethylsilyl enol ether of *iso*-butyraldehyde **54**, in the presence of the Lewis acids $TiCl_4$ and $Ti(O\textit{i}\text{-}Pr)_4$, gave the desired keto aldehyde **55** in 83 % yield as a 5.4:1 mixture of *trans* / *cis* isomers. Treatment of **55** under the second-generation annulation protocol furnished the oxygen-bridged bicycle **56** in 77 % yield as a single isomer. This was decarboxylated under Krapcho[39] conditions, then methylenated using the Tebbe protocol[40] to give **57**. The *exo*-olefin was isomerized to a mixture of endo-alkenes **58a** and **58b** as a 12:1 ratio favoring the desired **58a**, cleavage of whose bridging ether would afford dactylol.



Scheme 4.11: The Molander synthesis of (+)-dactylol.

This final step proved a problematic end to the synthesis. Molander originally investigated a model study of dactylol in which the structure synthesized lacked three of the four methyl groups (Scheme 4.12). The ether of this model substrate resisted cleavage under a host of conditions reported to cleave bridging ethers or allylic ethers, affording either a low yield of product, or undergoing no reaction at all. This observation was consistent with that reported by Rigby for cleavage of a similar bridging ether.[41] In the event, the model substrate eventually afforded the ring-cleaved product **61** in 45 % yield upon dissolving metal reduction. When this step was conducted in the actual synthesis, (+)-dactylol was recovered in only 25 % yield, along with the reduced compound **59** in 36 % yield. The Molander synthesis displayed an effective use of the [5+3] annulation approach to the synthesis of the oxygen-bridged, fused bicyclic system. As was seen in the Gadwood synthesis, the conformational preferences in the cyclooctanoid resulted in a problematic step late in the synthesis.

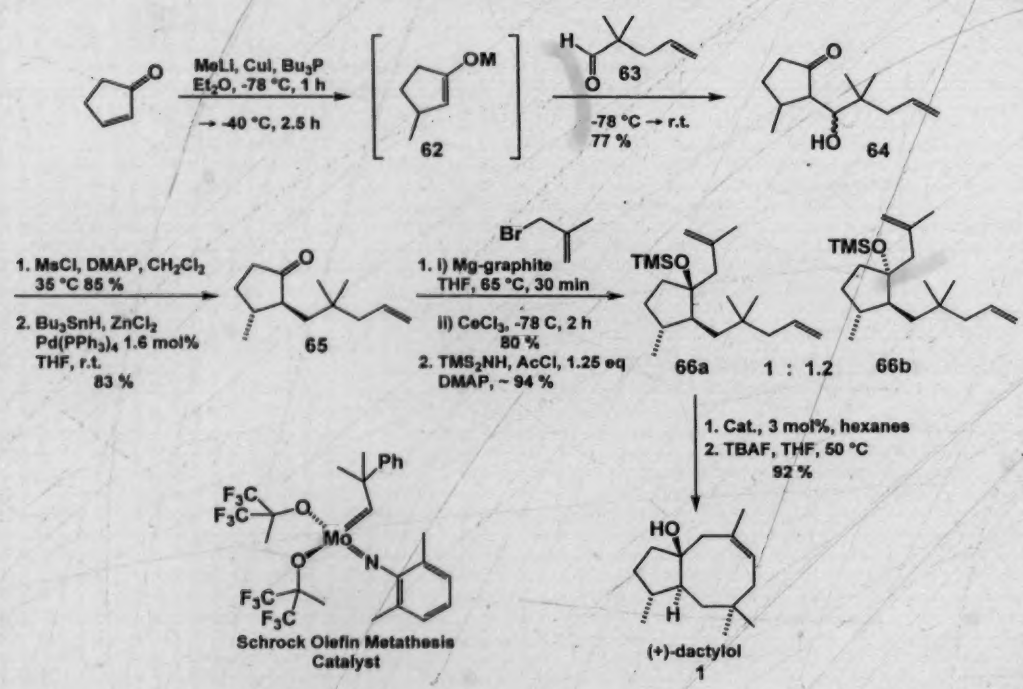


60 61

Scheme 4.12: The model study by Molander for the cleavage of a bridging ether.

4.2.7. The Fürstner Synthesis of Dactylol

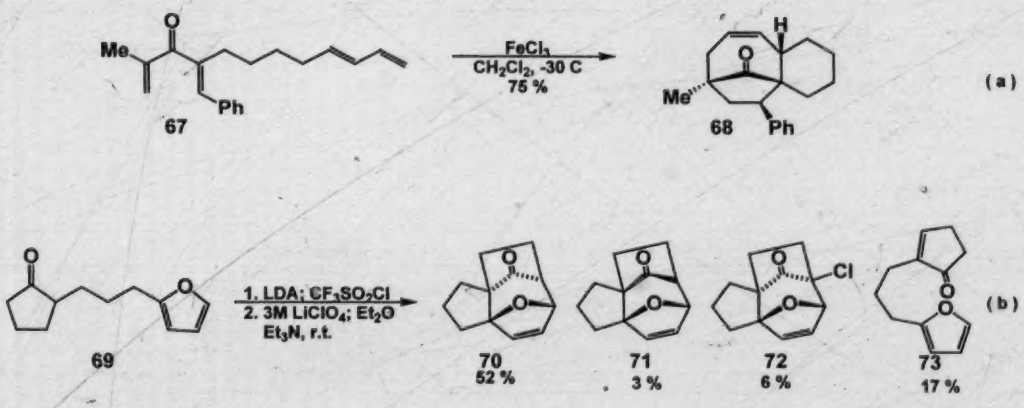
Given the advancements in the area of ring closing olefin metathesis for the synthesis of medium sized rings,[42] the natural product dactylol proved a simple synthetic target for Fürstner and Langemann.[43] In 1996 they disclosed the rapid, straightforward synthesis of this natural product which began with a three component coupling developed by Suzuki (Scheme 4.13).[44] Conjugate addition of methyl cuprate into cyclopentenone gave enolate **62**, which was treated with aldehyde **63** providing alcohol **64** in 77 % yield. This alcohol was converted to the corresponding mesylate, which was eliminated, and the resulting olefin reduced chemoselectively to give **65** in 83 % yield. The organocerium reagent[45] derived from methallyl bromide was added into the carbonyl of **65**, and the resulting alcohol was protected as a trimethylsilyl ether, affording a 1.2 : 1 mixture of **66a** and **66b**, favoring the undesired isomer. Compound **66a** was treated with the Schrock molybdenum catalyst,[46] which afforded dactylol in 92 % yield (upon removal of the silyl protecting group). This was a six step synthesis of dactylol, proceeding in 17 % overall yield, which proved a predictable application of the very powerful ring closing metathesis methodology.



Scheme 4.13: The Furstner synthesis of dactylol.

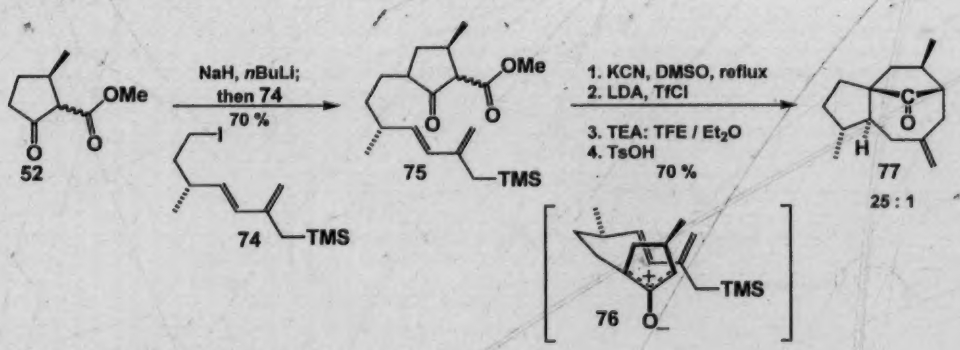
4.2.8. The Harmata Synthesis of (+)-Dactylol

The final dactylol synthesis found in the literature was published by Harmata and co-workers.[47] Earlier reports of [4+3] cycloadditions providing fused bicyclic carbocycles were published by West[48] and Harmata (Scheme 4.14).[49] Though these substrates afforded the products in good yield, they sometimes also suffered from poor stereoselectivity (Scheme 4.14, eq. b). While investigating the factors that influence the stereochemical outcome of this reaction, Harmata conducted a total synthesis of (+)-dactylol.



Scheme 4.14: Representative examples of the intramolecular [4+3] cycloaddition.

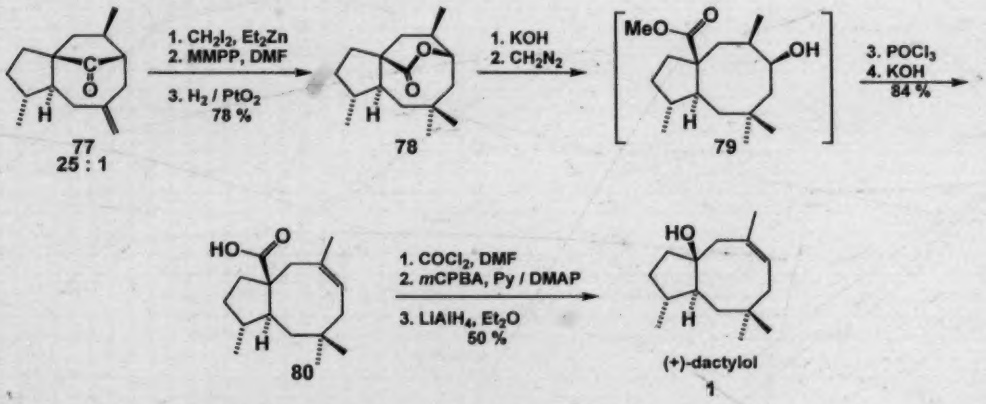
The cycloaddition precursor was prepared by alkylating the dianion of methyl pulegonate **52** with iodide **74**, affording **75** in 70 % yield (Scheme 4.15).[50] This was decarboxylated using the Krapcho conditions, then chlorinated with triflyl chloride.[51] The resulting chloroketone was exposed to a mixture of base, trifluoroethanol and ether to generate the zwitterion **76**, which underwent 4+3 cycloaddition (and subsequent protiodesilylation of the alkylsilane) in 70 % overall yield. Product **77** was formed as a 25:1 ratio of isomers, and the stereochemistry of **77** was consistent with the stereochemical model **76** proposed by the authors.



Scheme 4.15: The Harmata synthesis of (+)-dactylol, part 1.

Compound **77** was then converted into **78** in 78 % yield by a Simmons-Smith / Baeyer-Villiger / hydrogenolysis sequence (Scheme 4.16). Saponification, followed by

methyl esterification afforded intermediate **79**, which underwent dehydration then saponification to give acid **80**. Oxidative decarboxylation of **80** was accomplished by the carboxy inversion reaction.[52-54] Treatment of **80** with phosgene gave the acid chloride, which was converted into the mixed carbonate upon treatment with *m*CPBA. Reduction of this afforded (+)-dactylol in 50 % yield over the final three steps. Harmata has demonstrated the efficient generation the fused, bicyclic system of (+)-dactylol by employing the intramolecular [4+3] cycloaddition.



Scheme 4.16: The Harmata total sunthesis of (+)-dactylol.

4.3. Results and Discussion

4.3.1. Preliminary Considerations

These syntheses have highlighted several of the methods by which fused cyclooctanoids can be prepared. Included was the cycloheptanoid ring expansion, the anionic oxy-Cope rearrangement, and the intramolecular [5+2] photo-cycloaddition. Also seen was the use of ring-closing metatheses, the [5+3] annulation and the [4+3] cycloaddition. In most instances, the synthesis of dactylol served as either a biosynthetic probe, or a means by which novel chemistries could be employed in synthesis. What was also observed in selected cases were unexpected reactivities, or lack thereof, of late-stage cyclooctanoid intermediates. Examples of this include the unwanted hemi-ketalization

seen by Gadwood, the problematic Baeyer-Villiger reaction encountered by Feldman and the difficult ether cleavage encountered by Molander. These reactivities were typically attributed to the conformational preferences of 8-membered rings, and were only encountered subsequent to the effective use of protocols which afforded the fused, medium-sized rings.

The methodology developed in our research group for the synthesis of fused, medium-sized rings by the heteroatom-stabilized Stevens [1,2]-shift of oxonium ylides was presented in Chapter 2. We showed that such carbocyclic frameworks are prepared in relatively few steps from simple starting materials, and the key Stevens [1,2]-shift was shown to be a high yielding, diastereoselective process. Additionally, we showed that the remote sulfide resulting from the sulfur-stabilized [1,2]-shift could trigger cleavage of the bridging ether in high yield upon reductive desulfurization. Based on these results, the original study by Dr. F. P. Marmsäter[55] can be seen as a model study on the synthesis of (+)-dactylol, having prepared a model compound which lacked the four methyl groups.

As in the previously discussed examples, we set out to showcase this novel methodology in a total synthesis. We believed the Stevens [1,2]-shift protocol was well suited to this target, and that the sulfur-triggered cleavage of the bridging ether would help to circumvent one of the potential late-stage problems. The acetal-tethered cyclopentanone was derived from methyl pulegonate **52**, which was employed in both the Molander and Harmata syntheses. However, as with others, we still encountered late-stage transannular reactions that required several variations of the synthesis to be investigated. Our efforts toward this end will be presented in the following sections.

4.3.2. The Retrosynthesis

As suggested above, the investigation by Dr. F. P. Marmsäter (see Chapter 2) proved to be a model study on the synthesis of (+)-dactylol, resulting in a model compound lacking the four methyl groups. To complete the total synthesis, we were required to devise a method by which these methyl groups could be incorporated into the

existing reaction sequence. A retrosynthetic analysis of our intended sequence is seen in Figure 4.3. The target was to come from intermediate **81** via oxidation with allylic transposition, geminal dimethylation and reduction of a carbonyl to saturation. Intermediate **81** was to result from a sequence of sulfur-triggered bridging ether cleavage and methyl addition into the carbonyl of compound **82**. From intermediate **82**, the chemistry is analogous to the methods previously developed for the formation of oxygen-bridged, fused medium-sized rings. Bicycle **82** was expected to arise from the sulfur-assisted Stevens rearrangement of mixed thioacetal **83**, which was to come from acetal **84**, using the standard methodology. We believed acetal **84** to be available from methyl pulegonate **52**, which was shown in the Molander synthesis to be available from (+)-pulegone **51** in three steps.

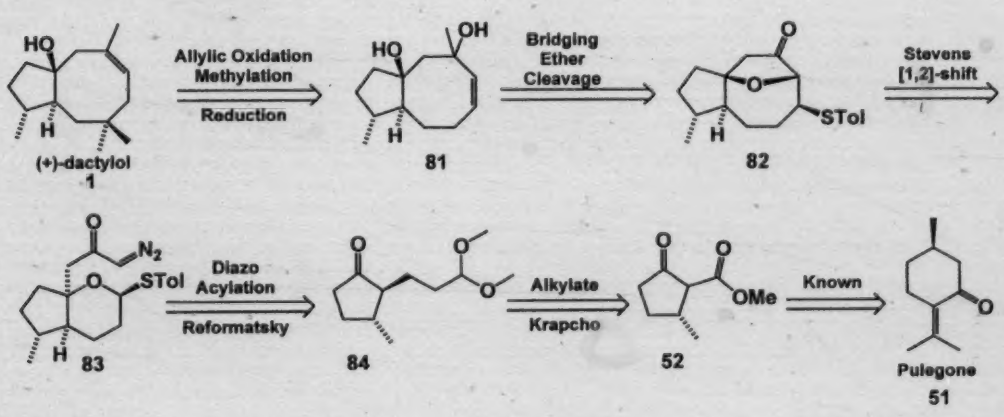
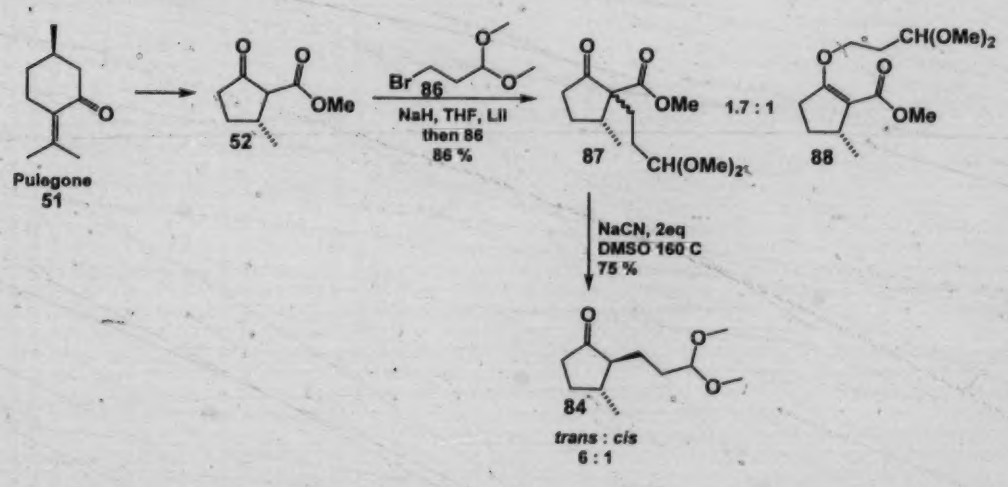


Figure 4.3: The retrosynthetic analysis of (+)-dactylol.

4.3.3. The First Generation Approach to (+)-Dactylol

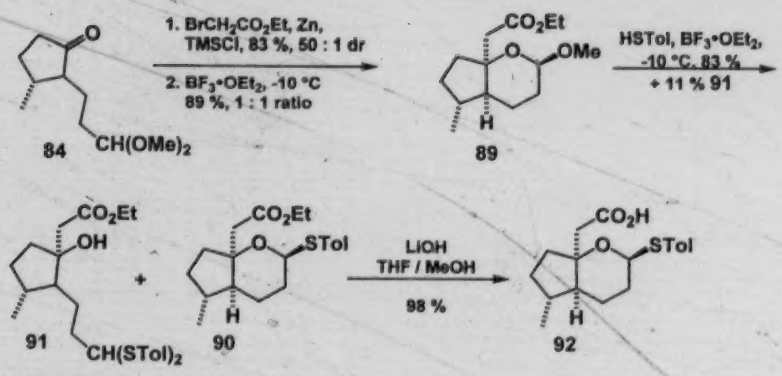
The synthesis began with (+)-pulegone **51**, affording **52** in the same three steps as in the Molander synthesis (Scheme 4.17). Treatment of **52** with NaH, followed by bromoacetal **86** afforded a 1:1.4 mixture of the C- and O-alkylated products **87** and **88**, respectively. To minimize the occurrence of **88**, we attempted to match the hard / soft nature of the alkylating agent and the substrate. By conducting the alkylation in the presence of two equivalents of LiI, the alkylation process was doubly benefitted. First,

acetal **86** underwent an in situ Finkelstein halogen exchange to the iodide, which is a softer electrophile, and more closely matched with the carbon nucleophile in terms of hard / soft arguments. Secondly, lithium ions make more covalent enolates than do sodium ions, further promoting for the C-alkylation product **87**. In the event, the alkylation afforded a 1.7 : 1 mixture of **87** and **88** in 86 % yield. The subsequent Krapcho decarboxylation[56] occurred without incident, affording the desired product **84** in 75 % yield, as a 6 : 1 ratio favoring the desired *trans* isomer.



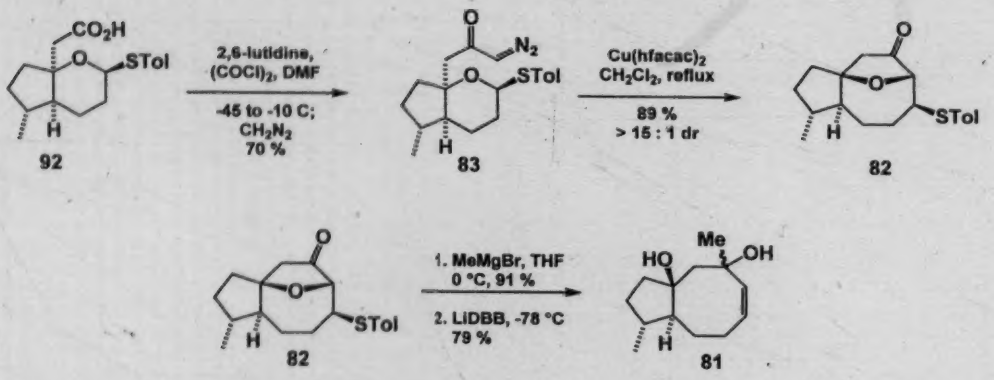
Scheme 4.17: Toward the synthesis of (+)-dactylol, beginning with (+)-Pulegone.

Acetal **84** was treated under the standard Reformatsky[57] conditions, giving the alcohol in 83 % yield, in a 50:1 dr, and this was treated with $BF_3 \bullet OEt_2$ to give the mixed acetal **89** as a 1:1 ratio of α and β anomers in 89 % yield, as well as an occasional trace of the vinyl ether (Scheme 4.18). Thio exchange occurred to give the mixed thioacetal **90** in 83 % yield, with an additional 11 % of the dithioacetal **91**. Saponification of **90** gave carboxylic acid **92** in near quantitative yield.



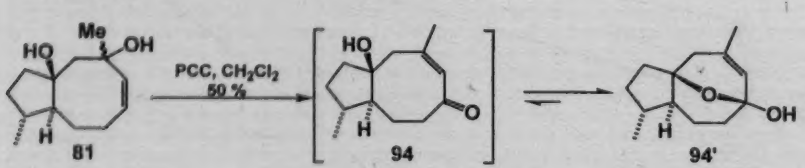
Scheme 4.18: Mixed thioacetal formation and ester saponification.

Carboxylic acid **92** was converted into the diazoketone **83** via the new protocol developed in Chapter 2, giving **83** in 70 % yield (Scheme 4.19). Treatment of this diazoketone with the catalyst $Cu(hfacac)_2$ in refluxing dichloromethane afforded the product **82** from the sulfur-stabilized Stevens rearrangement in 89 % yield, with 15 : 1 diastereoselectivity favoring migration with retention of configuration. This further showed that the [1,2]-shift of oxonium ylides is effective in generating the oxygen-bridged, fused bicyclic skeletons in good yield, with good diastereoselectivity. In continuing with the synthesis, we noted that methyl substitution was required at the site of the current carbonyl. Because removal of the carbonyl functionality prior to reductive desulfurization was desirable in any case, **82** was subjected to MeMgBr to yield the tertiary allylic alcohol as a single diastereomer. Treatment with LiDBB then afforded diol **81** in 79 % yield.[58,59]



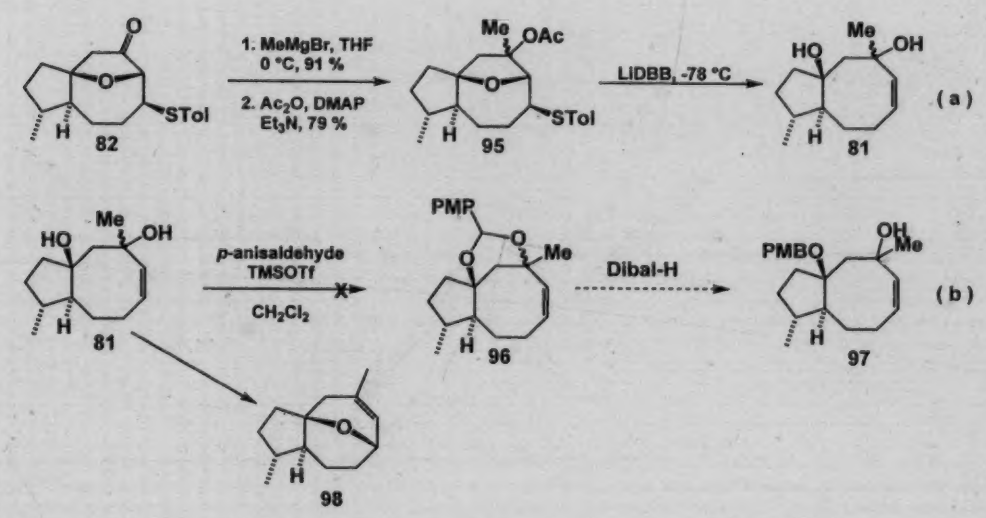
Scheme 4.19: The Stevens [1,2]-shift and the reductive desulfurization.

In order to complete the synthesis, all that remained was to effect oxidation with allylic inversion,[60] insert the geminal dimethyl substitution and reduce the carbonyl to saturation, affording (+)-dactylol. In the event, diol **81** was treated with PCC in methylene chloride and it underwent the oxidation to give enone **94** in 50 % yield (Scheme 4.20). In analyzing the NMR spectra of the product, we found that this preferred to exist as the transannular hemi-ketal, similar to the situation observed by Gadwood.[20] We were aware of his observation prior to commencing our synthesis, and we proceeded on the assumption that formation of the 6-membered hemi-ketal would be less favorable than formation of the 5-membered hemi-ketal **31** isolated by Gadwood. To our dismay, it appeared that conformational preferences in **94** allowed hemi-ketal formation to be a favorable process. Our inability to coerce any enolate reactivity from this substrate suggested that the equilibrium, if it exists at all, lies far to the side of hemi-ketal **94'**. As a result, this approach was deemed unworkable.



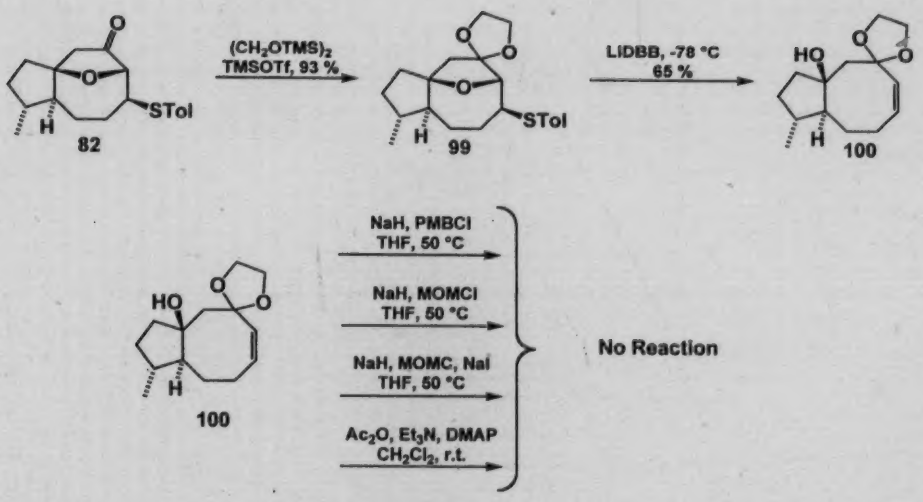
Scheme 4.20: Oxidation with allylic inversion: transannular hemi-ketal formation.

Several attempts were made to circumvent this problem by selectively protecting the alcohols of **81** (Scheme 4.21). The carbonyl of **82** was methylated, and the resulting alcohol protected as the acetate, giving **95** as a single diastereomer in 79 % yield. We hoped to have **95** undergo the reductive ether cleavage, and then protect the resulting tertiary alcohol. However, upon treatment of **95** with LiDBB ether cleavage occurred with concomitant acyl deprotection to give diol **81**. We subsequently attempted to protect diol **81** as the benzylidene acetal of *p*-anisaldehyde **96**. It was hoped that this might undergo selective reduction by Dibal-H to afford predominantly **97**. However, upon treatment of **81** with *p*-anisaldehyde in the presence of a Lewis acid, the diol underwent an acid-catalyzed dehydrative etherification to afford **98**.



Scheme 4.21: Attempts at protecting the alcohols as acetate or acetal.

We next attempted to protect the bridgehead alcohol prior to formation of the second alcohol (Scheme 4.22). Hence, the carbonyl of **82** was converted into the corresponding dioxolane **99** in 93 % yield, and this was subjected to the reductive desulfurization protocol, affording alcohol **100** in 65 % yield. We then attempted to protect this alcohol as an acetate, as a benzyl- or methoxymethyl ether, all to no avail.



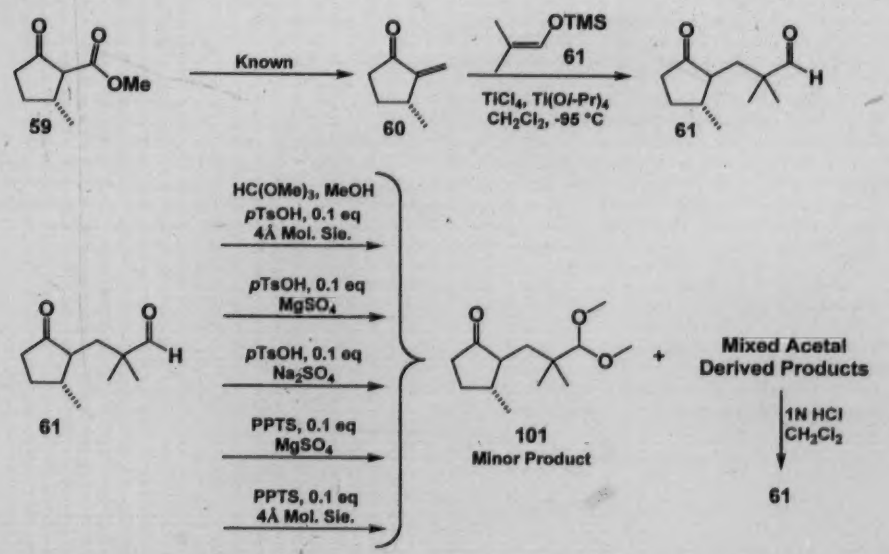
Scheme 4.22: Attempts to protect the bridgehead alcohol.

Based on this lack of reactivity, we concluded that routes requiring the protection of this alcohol would not be feasible, and so the proposed synthetic sequence would require extensive modification. To this point we had demonstrated that the Stevens [1,2]-shift proceeded as anticipated, affording the desired oxygen-bridged bicycle, as did the sulfur-triggered ether cleavage, providing the desired bridgehead alcohol. The last handful of transformations in the overall synthesis was designed to enable incorporation of the geminal dimethyl substituents. Given this, we believed that by conducting these at the outset of the synthesis, we could avoid undesirable late-stage transannular processes.

4.3.4. The Second Generation Approach to (+)-Dactylol

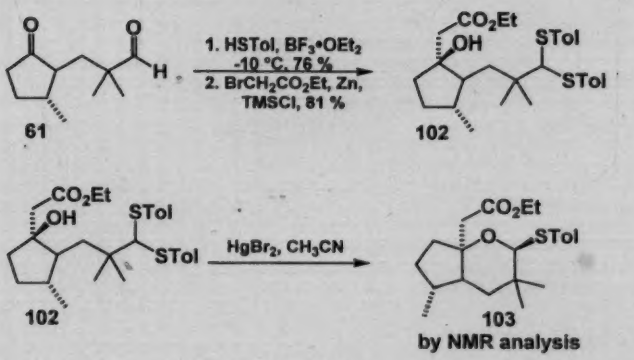
We subsequently decided to employ the same initial sequence used by Molander and co-workers in their synthesis of (+)-dactylol.[31] Keto ester **52** was converted into enone **53**, and then on to keto aldehyde **54** by the sequence shown in Scheme 4.11. Numerous attempts were made to selectively generate the dimethyl acetal **101** employing a combination of acid catalysts and dehydrating agents (Scheme 4.23). In all cases, the desired acetal **101** was isolated as a minor product. The rest of the mass balance

consisted of mixed acetal-derived products, treatment of which with dilute aqueous acid afforded the keto aldehyde **61**.



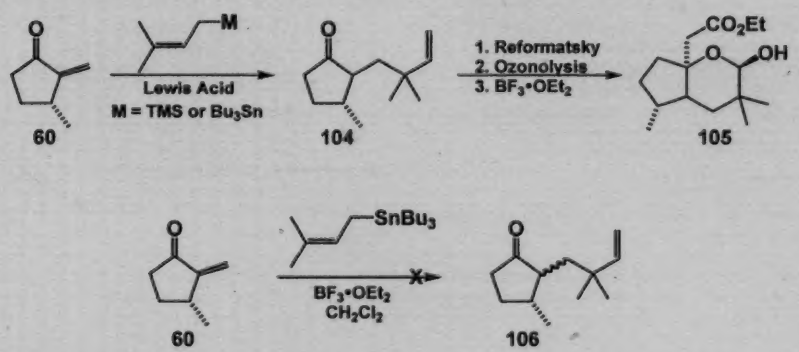
Scheme 4.23: Dimethyl acetal formation in the presence of a ketone was ineffective.

In contrast to the dimethyl acetal **101**, the dithioacetal was prepared with ease in 76 % yield, and this was subsequently treated under the Reformatsky conditions to afford alcohol **102** in 81 % yield (as an undetermined mixture of diastereomers) (Scheme 4.24). Ring-closure to the mixed thioacetal could apparently be effected using $HgBr_2$ activation. However, the resulting product **103** was formed as a complex mixture of diastereomers, and this approach was not pursued further.



Scheme 4.24: Dithioacetal formation in the presence of a ketone was effective.

We next investigated the possible addition of a prenylsilane or stannane into enone **60** (Scheme 4.25). Such a process would afford compound **104**, which could function as a masked aldehyde. Were compound **104** first subjected to a Reformatsky reaction, followed by an ozonolyis of the terminal alkene, and finally subjected to a Lewis acid mediated hemi-acetal formation, the original synthetic pathway would be valid from **105**. In the event, treatment of **60** with prenyltributyltin[61] and $BF_3 \bullet OEt_2$ afforded a mixture of products. Characterization of the products proved difficult as the vinyl and methyl signals were eclipsed by the unreacted prenyltributyltin. Numerous attempts were made to prepare the analogous silane employing literature procedures,[62-64] but none of these worked, so this investigation was abandoned.



Scheme 4.25: Prenyltributyltin addition into enone **60**.

4.3.5. The Third Generation Approach to (+)-Dactylol

At this point we chose to simplify the synthetic sequence, accepting that incorporation of the geminal dimethyl groups at the beginning of the synthesis would not be as facile as predicted. It is known that geminal dimethyl substitution can be incorporated into a molecule via cyclopropanation of an exocyclic olefin, followed by hydrogenolysis with Adams catalyst.[7-9] This sequence was found in the latter portion the Harmata synthesis of (+)-dactylol, and we believed this to be a viable alternative to the methods already investigated. Should keto ester **52** be alkylated with bromide **107**,[65] and the resulting product **108** be subjected to the Krapcho decarboxylation conditions, it would afford acetal **109** (Figure 4.4). Subjection of **109** to the cyclopropanation / hydrogenolysis sequence would then afford the desired diethyl acetal **110**.

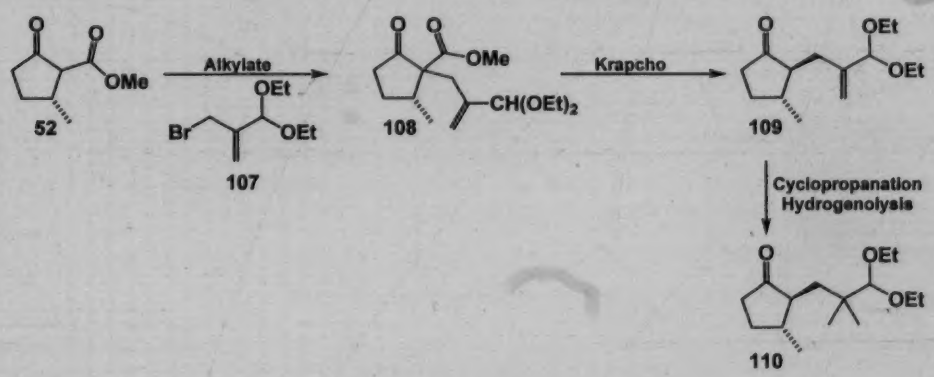
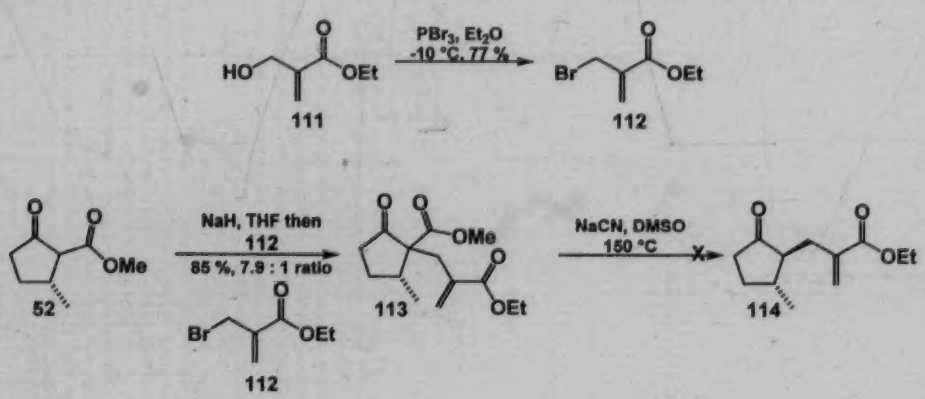


Figure 4.4: Incorporating the geminal dimethyl groups via cyclopropanation / hydrogenolysis.

During the first synthesis of **107**, alcohol **111** was prepared by the Baylis-Hillman reaction between ethyl acrylate and *para*-formaldehyde.[66] Treatment of this with PBr_3 afforded the allyl bromide **112** in 77 % yield (Scheme 4.26).[67] Keto ester **52** was treated with NaH, and then **112**, which afforded the alkylation product **113** in 85 % yield as a 7.9 : 1 ratio of diastereomers. Unfortunately, all attempts to effect the Krapcho

decarboxylation on **113** failed to afford **114**. Prolonged heating in the presence of NaCN resulted only in decomposition of the starting material. Various trials were attempted using a Biotage microwave reactor, in the hope that the high temperatures achieved over a relatively short timeframe might be beneficial. However, in no instance was the product observed. The inability of this substrate to undergo the Krapcho decarboxylation suggested that this might also be a problem upon synthesizing adduct **108** as well. Because of this, we investigated methods by which diethyl acetal **109** could be prepared indirectly from **52**, employing a transesterification / Carroll rearrangement sequence, which would permit the rapid synthesis of **110**. Upon transesterification of **52** with alcohol **115**, the keto ester **116** would be heated in a polarizing solvent to enable enolization. Should this occur to the side of the ester (as in **117a**), a [3,3]-sigmatropic rearrangement could take place, affording **109** upon subsequent decarboxylation of **117b** (Figure 4.5).



Scheme 4.26: Alkylation of **52** with ethyl 2-bromomethylacrylate.

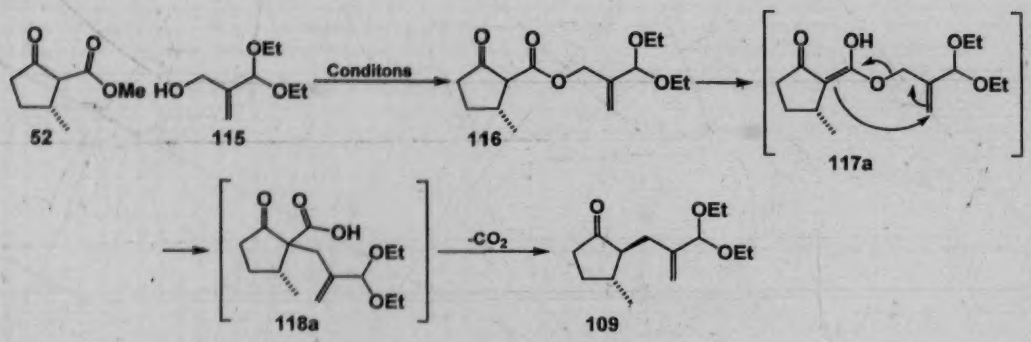
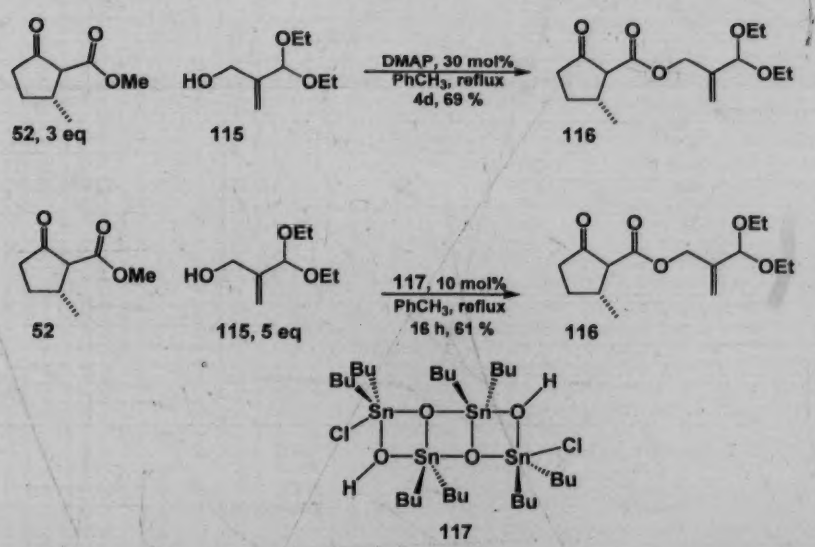


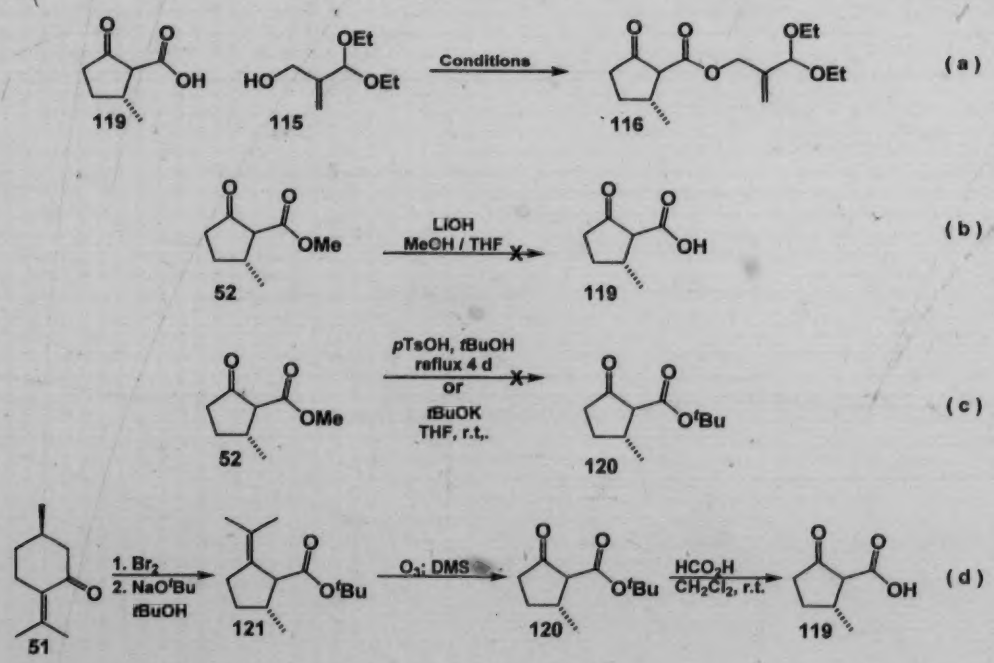
Figure 4.5: The transesterification / Carroll rearrangement sequence.

Two transesterification protocols were investigated. First the alcohol **115** and the keto ester **52** were combined in toluene, in the presence of DMAP, and heated over prolonged periods of time (Scheme 4.27).[68, 69] Alternatively, they were sealed together, and subjected to microwave irradiation. The preparation of **116** were found to require 3 equivalents of the chiral ester **52**, and refluxing in toluene for 4 days. Because these were not desirable reaction conditions, we subsequently prepared the Otera transesterification catalyst (**117**), which proved effective at promoting allyl transesterification.[70, 71] We had hoped this protocol would afford better yields of **116** in shorter reaction times. In the event, compounds **52** and **115** were combined with the catalyst and heated overnight in toluene. From this, **116** was isolated in 61 % yield. The drawback to this protocol was the need for greater than 5 equivalents of alcohol **115** for the method to be effective. Both of these protocols were found to be moderately effective at promoting the transesterification, though each required large excesses of one of the reagents.

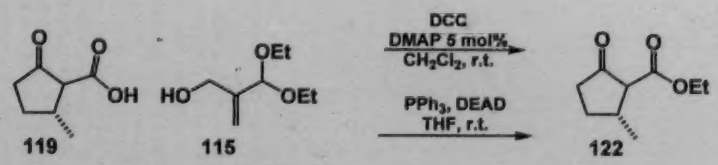


Scheme 4.27: Synthesis of the Carroll rearrangement substrate by transesterification.

This need for excess reagent was deemed unacceptable, and we sought a protocol by which the coupling partners could be combined in a 1 : 1 ratio. We envisioned the esterification of acid **119** might be possible (Scheme 27, eq. a). After numerous attempts, it was determined that acid **119** could not be generated directly by saponification of keto ester **52** (Scheme 28, eq. b). We then elected to generate this by the formic acid-mediated deprotection of *t*-butyl ester **120**. After direct *t*-butyl transesterification[72, 73] from **52** proved unsuccessful (Scheme 4.28, eq. c), the *t*-butyl ester **120** was prepared from (+)-pulegone **51** (Scheme 4.28, eq. d). After treating **51** with bromine, the resulting dibromide was added into a solution of NaO*t*Bu in *t*BuOH, and stirred overnight, which afforded **121** in 47 % yield. This then underwent ozonolysis to give the desired *t*-butyl ester **120** in 87 % yield, which gave the desired carboxylic acid **119** in 92 % yield upon treatment with formic acid in CH_2Cl_2. The esterification of acid **119** with alcohol **115** was attempted by both DCC / DMAP mediated coupling, and the PPh_3 / DEAD mediated protocol (Scheme 4.29). In both cases, none of the desired product **116** was isolated. We surmised that the acetal decomposed under the reaction conditions, as the main product isolated from these reactions was the known ethyl ester **122**.



Scheme 4.28: Synthesis of the β-keto acid **119**.

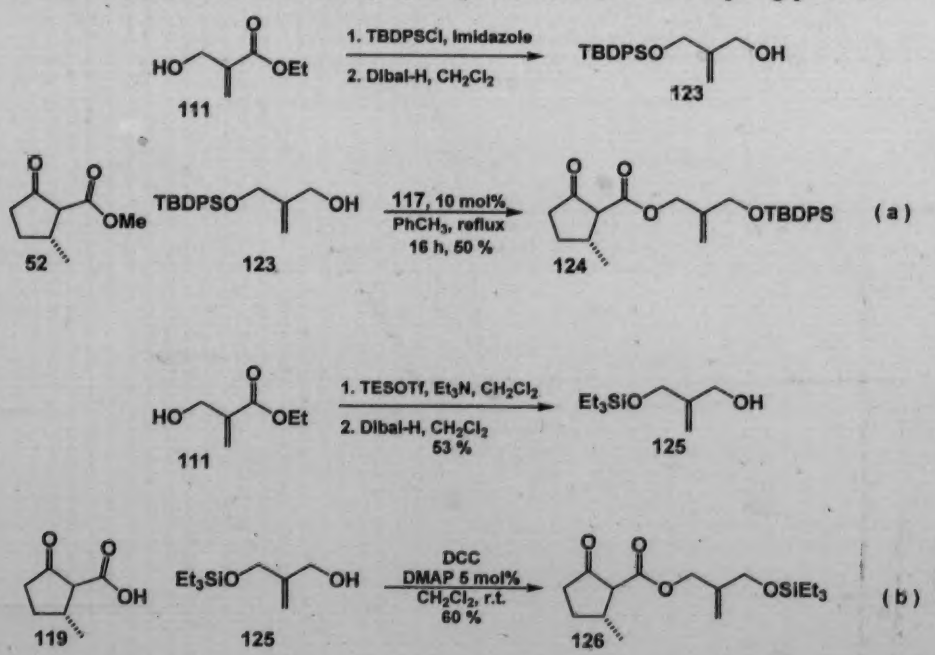


Scheme 4.29: Esterification of acid **119** proves unsuccessful with alcohol **115**.

Once again, the generation of **116** via a coupling protocol was found to be ineffective. In fact, all three methods attempted for the generation of ester **116** had their drawbacks. The DMAP-mediated coupling required lengthy reaction times and a 3-fold excess of the chiral keto ester **52**. The protocol employing the Otera transesterification catalyst required a 5-fold excess of the costly alcohol **115** in order to be effective. Finally, the esterification of acid **119** resulted in decomposition of the alcohol **115**. Thus all three of these methods fell short of our expectations. Because we still wished to

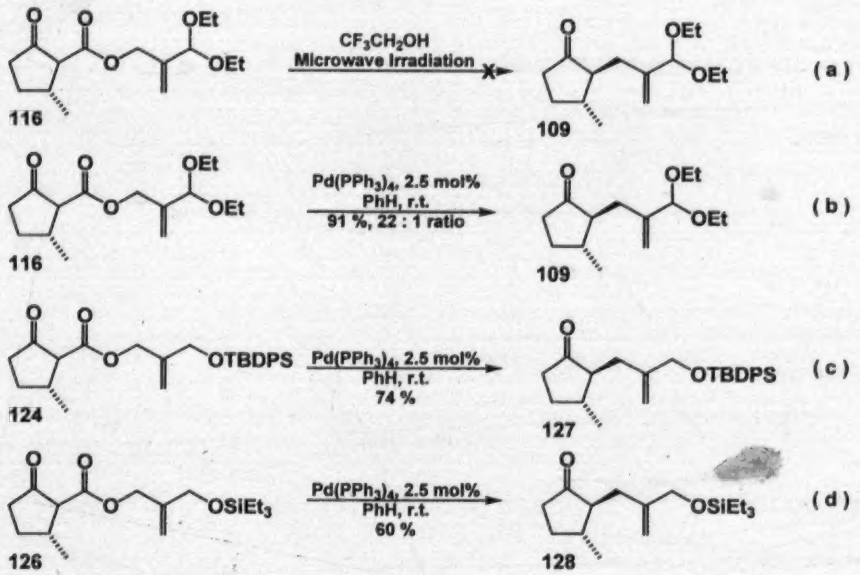
employ the transesterification / Carroll rearrangement protocol in the overall synthesis, a cheaper, more readily available variation of alcohol **115** was developed.

Alcohol **123** was prepared by TBDPS protection of alcohol **111**, followed by Dibal-H reduction of the ethyl ester (Scheme 4.30).[74] Transesterification between **52** and **123** using the Otera catalyst **117** afforded the desired product **124** in 50 % yield. The low yield is attributed to the fact that the bulky silyl protecting group impedes approach of the alcohol to the catalyst-acid complex.[71] Because of this, a second alcohol **125** was also prepared by the sequence above, affording TES-protected alcohol (Scheme 4.30, eq. b). At this time, we believed the DCC-mediated coupling might be effective as there was no longer an acetal to be decomposed. In the event, alcohol **125** was treated with acid **119** and DCC, which furnished the transesterified product **126** in 60 % yield. Though this reaction was found to proceed in only 60 % unoptimized yield, we were gratified to have found a method that did not employ large excesses of one coupling partner.



Scheme 4.30: Preparation of the silyl-protected alcohols for use as alternative coupling partners.

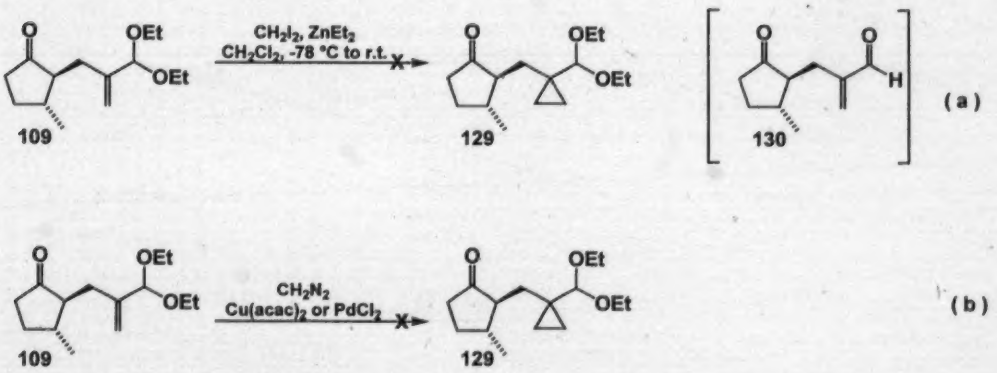
Throughout the transesterification investigation, three substrates were prepared, **116**, **124** and **126**, all potential substrates for the Carroll rearrangement. Preliminary investigations into effecting the rearrangement of **116** by microwave irradiation (in a polarizing solvent) afforded decomposed starting material (Scheme 4.31, eq. a). At this time, we found several literature precedents that indicated that treatment of allyl β-keto esters with a palladium (0) catalyst in benzene could effect a decarboxylative allylation.[75-80] Treatment of **116** under these conditions, with 2.5 mol% of $Pd(PPh_3)_4$, afforded the desired product **109** in 91 % yield, as a 22 : 1 ratio of isomers (Scheme 4.31, eq. b). Compound **124** was next subjected to these conditions, affording product **127** in 74 % yield (eq. c). Lastly, **126** was subjected to these conditions, which afforded **128** in 60 % yield (eq. d).



Scheme 4.31: The palladium-catalyzed decarboxylative allylation.

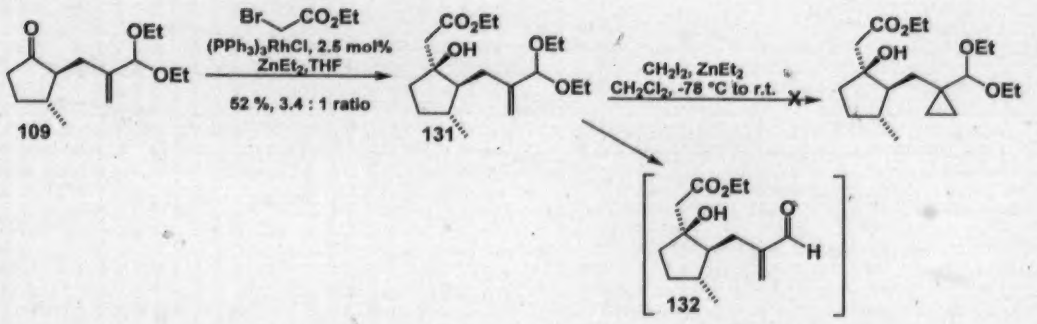
Having at last prepared the desired acetal **109**, we attempted to convert this into the geminal dimethyl substrate **110**. Treatment of **109** under Simmons-Smith cyclopropanation conditions afforded a mixture of recovered **109**, as well as aldehyde **130**, but none of cyclopropane **129** was isolated (Scheme 4.32, eq. a). Though **130** was

not fully characterized, its identity was proposed based on the observation of a new aldehyde peak in the ^{1}H NMR spectrum, as well as a 1 ppm downfield shift of the alkene protons. The cyclopropanation was also attempted using diazomethane, under either palladium or copper catalysis, but only **109** was recovered from the reaction (Scheme 4.32, eq. b).



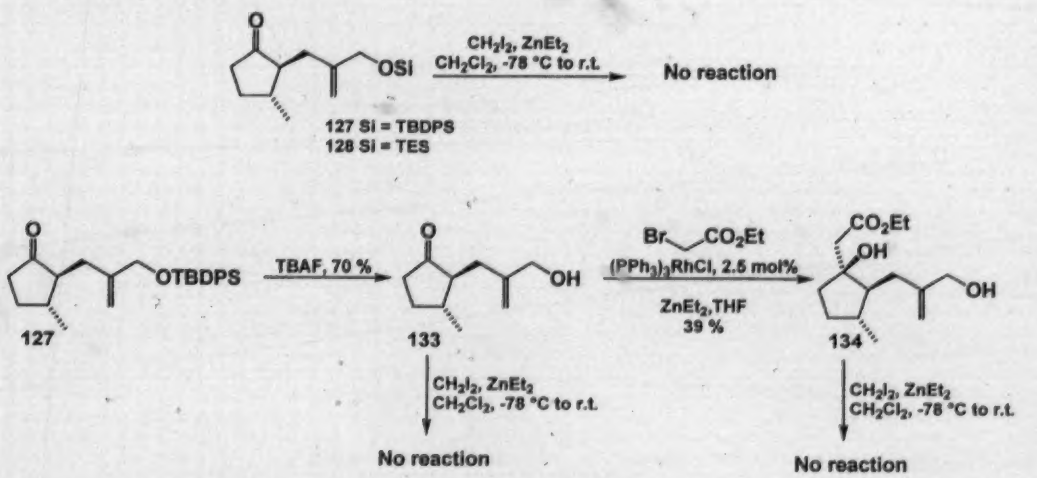
Scheme 4.32: Attempted cyclopropanation of a diethylacetal **109**.

Acetal **109** was then subjected to the Reformatsky reaction conditions, which afforded the desired alcohol **131** in 52 % yield as a 3.4 : 1 ratio of isomers (Scheme 4.33). We next attempted the Simmons-Smith cyclopropanation of **131**, believing the directing effect of the tertiary alcohol might be to our benefit. In the event, it again appeared that the acetal decomposed to give aldehyde **132**, as changes similar to that described above were observed in the ^{1}H NMR spectrum. Once again, the diethyl acetal functionality on the molecule proved problematic in advancing the synthesis toward (+)-dactylol. Given these unresolved issues, we elected to abandon (for the present time) the heteroatom stabilized Stevens [1,2]-shift approach, because it appeared that the acetal functionality was detrimental to the sequence.



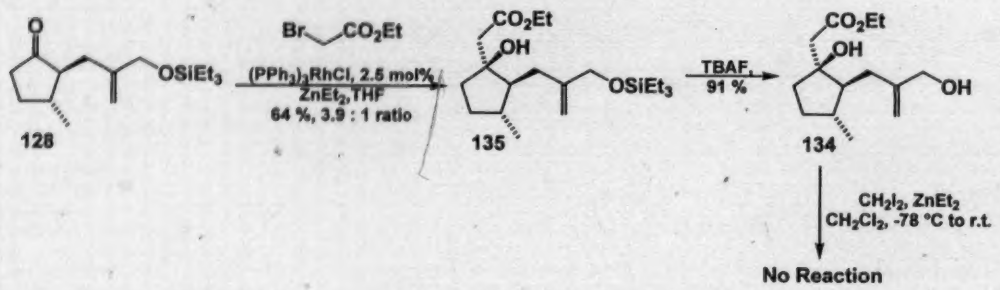
Scheme 4.33: Reformatsky addition, followed by attempted cyclopropanation on **109**.

We elected to carry products **127** and **128** forward in the synthesis (Scheme 4.34). The Simmons-Smith cyclopropanation attempted on both of these substrates failed, affording only recovered starting materials. The TBDPS protecting group of **127** was removed upon treatment with TBAF to give alcohol **133** in 70 % yield, which was then treated under the cyclopropanation conditions. Again we believed the directing effect of the free alcohol would be to our benefit, and again the reaction failed to occur. Compound **133** was subjected to the Reformatsky reaction conditions, which afforded diol **134** in 39 % yield. The modest yield in this case was attributed to the presence of a free alcohol in **133**.



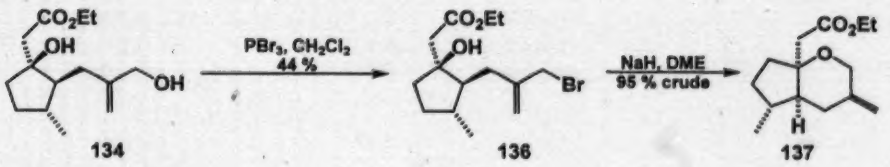
Scheme 4.34: The attempted cyclopropanation on alcohol **133** and diol **134**.

Accordingly, TES protected **128** was subjected to the Reformatsky conditions which afforded **135** in 64 % yield (BORSM) as a 3.9 : 1 mixture of isomers (Scheme 4.35). Alcohol **135** was then desilylated with TBAF, giving diol **134** in 91 % yield. Diol **134** was subjected to the Simmons-Smith reaction conditions, on the assumption that the directing effect of the allylic diol would finally afford the cyclopropanated product. In the event, the reaction again returned only starting material. (Note: A control experiment was conducted at various stages throughout the cyclopropanation trials in which cinnamyl alcohol was cleanly converted to the cyclopropane in good yield.)



Scheme 4.35: Attempted cyclopropanation on the allylic diol failed.

As a final resort, we elected to carry forward with the synthesis in hope of installing the geminal dimethyl group at a later stage in the synthesis, as did Harmata. Diol **134** was treated with PBr_3 to give allyl bromide **136** in 44 % yield (Scheme 4.36).[67] This was then treated with NaH in DME to give the allyl ether **137** in 95 % crude yield, along with an unquantified amount of the open-chain allyl bromide derived from the minor isomer obtained in the Reformatsky reaction. This material is apparently much slower to cyclize under the alkylation conditions, due to the greater strain of the resulting *trans*-oxabicyclo[4.3.0] nonane ring skeleton. Although this result was promising, time constraints prevented any further work on this approach.



Scheme 4.36: Closing the ether by alkylation. A new approach to (+)-dactylol.

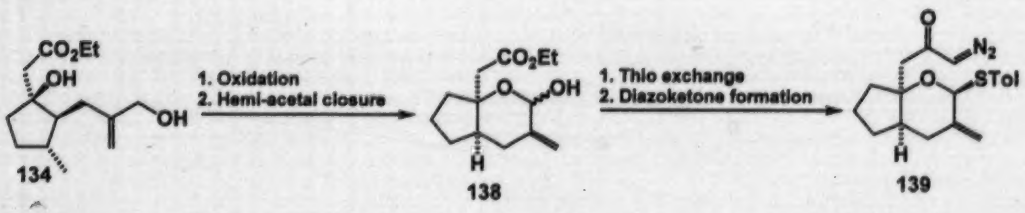
4.4. Conclusions and Future Work

Our efforts toward the total synthesis of (+)-dactylol have been presented. We showed that the novel protocol developed for the synthesis of fused, oxygen-bridged bicycles was an effective manner by which the bicyclic core of dactylol could be attained. We further demonstrated that the pendant sulfide moiety could trigger cleavage of the bridging ether, affording the requisite bridgehead alcohol upon reductive desulfurization. In the latter stages of our synthesis, while trying to install the geminal dimethyl substituents, we encountered a favorable transannular hemi-ketal formation, the product of which resisted all enolate reactivity. Our efforts to circumvent this favorable hemi-ketal formation by selective protection of the substrate was met with limited success, and so several variations of the proposed synthetic route were investigated.

We realized that incorporation of the geminal dimethyl group at an earlier stage in the synthesis would be to our benefit. We tried to achieve this by intercepting the Molander synthesis at an early stage, but conversion of an aldehyde to a dimethyl acetal in the presence of a ketone proved very challenging. We elected to then focus our efforts on the synthesis of substrates possessing functionality that might readily be converted into the geminal dimethyl group. Numerous methods were investigated, and positive results were found within the decarboxylative allylation protocol, which generated three intermediates we believed might be promising. Unfortunately, all attempts at the cyclopropanation of these substrates (at various levels of functionalization) were unsuccessful. As a final effort, we showed that these intermediates can be carried further

into the synthesis, in hopes of effecting the cyclopropanation and hydrogenation at a later stage.

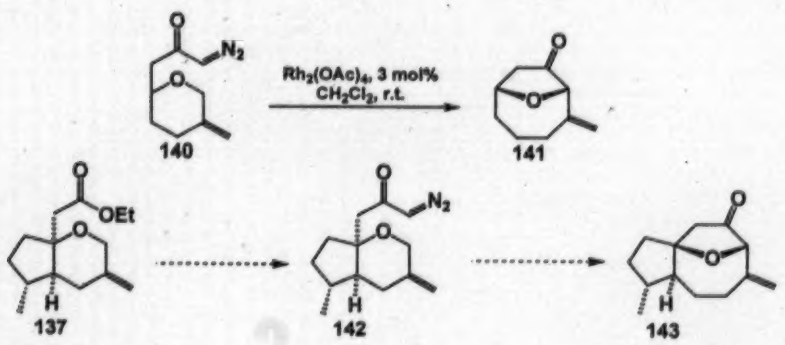
Though we strayed from the sulfur-stabilized Stevens [1,2]-shift toward the end of this campaign, the methodology developed last could still be employed in the mixed thioacetal route. It might be possible to effect an allylic oxidation on substrate **134**, which could conceivably close to the hemi-acetal **138** (Scheme 4.37). We never attempted the thio exchange reaction on a hemi-acetal substrate, but if this were to be effective we could conceivably continue with the original reaction sequence. One of the reasons we were reluctant to follow this route concerned the incorporation of the geminal dimethyl group. Should the cyclopropanation not be effective on the hemi-acetal, we could carry the synthesis forward, anticipating that it would be effective at a later stage. However, in order to reveal the geminal dimethyl group upon successful cyclopropanation, we would have to subject the substrate to hydrogenolysis. This would have to be a chemoselective process as every future intermediate in the reaction sequence between the mixed thioacetal and the final product would contain a potentially-reducible functional group.



Scheme 4.37: Final strategy in the sulfur-stabilized Stevens [1,2]-shift mediated synthesis.

The final substrate prepared is one that could conceivably be converted into the natural product, by way of a [2,3]-shift ring expansion. Our research group showed that a similar diazoketone-substituted pyran afforded an oxygen-bridged cyclooctanoid upon subjection to rhodium catalysis. If we were to convert **137** into the corresponding diazoketone **142**, and this were to undergo the rearrangement (as did **140** to give **141**), it would afford **143**. Because this molecule lacks the sulfide functionality that enabled the

cleavage of the bridging ether, it would be anticipated that cleavage of the bridging ether might prove difficult. Were this effective, the resulting bicycle might be converted into (+)-dactylol.



Scheme 4.38: The synthesis of (+)-dactylol via a [2,3]-sigmatropic rearrangement.

4.5. Experimental

4.5.1. General

Reactions were carried out in flame-dried glassware under a positive nitrogen atmosphere unless otherwise stated. Transfer of anhydrous solvents and reagents was accomplished with oven-dried syringes or cannula. Solvents were distilled before use: methylene chloride from calcium hydride, tetrahydrofuran and diethyl ether from sodium/benzophenone ketyl, toluene from sodium metal. Thin layer chromatography was performed on glass plates precoated with 0.25mm Kieselgel 60 F_{254} (Merck). Flash chromatography columns were packed with 230-400 mesh silica gel (Merck). Radial chromatography was carried out on a Chromatotron 7924T (Harrison Research) with plates prepared using silica gel 60 F_{254} with gypsum binder (EM) on glass rotors. Microwave irradiation was conducted using a Biotage Initiator.

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400 MHz or 500 MHz on Varian Inova 400 and 500, Mercury 400, or Unity 500 spectrometers,

and the chemical shifts are reported on the δ scale (ppm) downfield from tetramethylsilane. Coupling constants (*J*) are reported in Hz. Second order splitting patterns are indicated, though interpreted as if first-order. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; dd, doublet of doublets, etc. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 125 MHz and are reported (ppm) relative to the center line of a triplet at 77.23 ppm for deuterochloroform. Infrared (IR) spectra were measured with a Nicolet Magna 750 FT-IR infrared spectrophotometer. Mass spectra were determined on a Kratos Analytical MS-50 (EI) or Applied Biosystems Mariner Biospectrometry Workstation (ESI). Elemental analyses were obtained at the University of Alberta on a Carlo Erba CHNS-O EA 1108 Elemental Analyzer.

4.5.2. Substrate Syntheses

Bromo dimethyl acetal adducts 87 and 88. To a 100 mL round bottom flask was added sodium hydride (60 % dispersion in oil) (745 mg, 18.6 mmol, 1.1 equiv) which was rinsed with 15 mL of hexanes. The hexanes was decanted, and the flask charged with 13 mL of THF. To this stirred suspension was added a solution of **52** (2.64 g, 16.9 mmol, 1 equiv) in THF (10 mL) slowly over a period of 10 minutes, and the resulting mixture stirred at room temperature for a further 15 minutes, until all the sodium hydride was reacted. To this was then added a solution of 3-bromopropane-1,1-dimethyl acetal **86** (4.76 g, 20.6 mmol, 1.2 equiv) in THF (10 mL), followed by lithium iodide (2.48 g, 18.6 mmol, 1 equiv) and the resulting mixture was heated to reflux and stirred for 48 hours, or until the starting material was consumed. The reaction mixture was then cooled to r.t., diluted with diethyl ether (20 mL) and quenched with by the addition of saturated aqueous NH_4Cl (33 mL). The organic layer was separated and the aqueous layer extracted with diethyl ether (20 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, then concentrated to give the crude product as a yellow oil. This was then purified by gradient column chromatography (1, 2,

4, 8, 15, 25, 30 % EtOAc / hexanes) to give a mixture of **87** (2.29 g) and **88** (1.48 g) as a 1.7 : 1 ratio, respectively, as a yellow oil in an overall 86 % yield.

Isomer 87: R_f 0.39 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2956, 2831, 2679, 1749, 1732, 1455, 1404, 1385, 1329, 1290, 1229, 1193, 1165, 1127 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.28 (dd, J = 5.5, 5.5 Hz, 1H), 3.63 (s, 3H), 3.27 (s, 3H), 3.25 (s, 3H), 2.51 (dd, J = 19.0, 8.5 Hz, 1H), 2.25 – 2.11 (m, 2H), 2.03 (m, 1H), 1.89 – 1.82 (m, 1H), 1.79-1.68 (m, 3H), 1.47-1.39 (m, 1H), 1.01 (d, J = 6.8, Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.1, 170.9, 104.5, 62.4, 52.9, 52.4, 51.7, 40.0, 38.6, 28.1, 27.1, 26.7, 15.8; HRMS (ESY) calcd for $C_{13}H_{22}O_5Na$ (M+Na) 281.1359; found 281.1354.

Isomer 88: R_f 0.36 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2950, 2833, 1710, 1688, 1624, 1437, 1381, 1364, 1297, 1224, 1190, 1128 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.59 (dd, J = 5.7, 5.7 Hz, 1H), 4.04 (t, J = 6.4 Hz, 2H), 3.67 (s, 3H), 3.33 (s, 3H), 3.32 (s, 3H), 2.94 (m, 1H), 2.68 (dddd, J = 17.0, 10.8, 7.5, 1.8 Hz, 1H), 2.51 (ddd, J = 17.1, 9.7, 4.3 Hz, 1H), 2.05 (dddd, J = 12.7, 9.6, 8.4, 7.5 Hz, 1H), 1.98 (m, 2H), 1.42 (ddd, J = 17.0, 8.6, 4.2 Hz, 1H), 1.09 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 165.5, 109.8, 101.9, 66.3, 53.5, 53.5, 50.5, 36.6, 33.1, 29.7, 28.2, 20.8; HRMS (ESY) calcd for $C_{13}H_{22}O_5Na$ (M+Na) 281.1359; found 281.1356.

Dimethyl acetal 84. To a solution of **87** (2.29 g, 8.9 mmol, 1 equiv) in DMSO (90 mL) was added sodium cyanide (880 mg, 17.8 mmol, 2 equiv) and the resulting mixture heated to 155 °C for 35 min. This was then poured hot into saturated aqueous NH_4Cl (100 mL) and water (50 mL), and allowed to stir for 10 min.. This was then cooled, diluted with diethyl ether (200 mL), and the organic layer was separated. The aqueous layer extracted with diethyl ether (6 x 50 mL). The combined organic extracts were washed with water (4 x 50 mL), brine (100 mL), dried over $MgSO_4$, then concentrated. This was then purified by gradient column chromatography (1, 2, 4, 7, 14, 21% EtOAc / hexanes) to give 1.33 g of the desired product **84** as a 6 : 1 mixture of *trans* : *cis* isomers, respectively, in 75 % overall yield: R_f 0.50 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2954, 2872, 2829, 1738, 1459, 1407, 1381, 1271, 1224, 1191, 1155, 1125 cm^{-1}; ^1H NMR

(500 MHz, $CDCl_3$) δ 4.29 (dd, J = 5.4, 5.4 Hz, 1H), 3.26 (s, 3H), 3.25 (s, 3H), 2.32 – 2.24 (m, 1H), 2.08 – 1.98 (m, 2H), 1.83 (m, 1H), 1.75 – 1.67 (m, 1H), 1.61 – 1.50 (m, 4H), 1.39 – 1.29 (m, 1H), 1.10 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.5, 104.5, 56.0. 52.6, 52.6, 37.9, 36.8, 29.6, 29.5, 22.4, 19.5; HRMS (ESY) calcd for $C_{11}H_{20}O_3Na$ (M+Na) 233.1310; found 233.1311.

Mixed acetal 89. To a round bottom flask equipped with a magnetic stir bar and a reflux condenser, containing Zn dust (850 mg, 12.7 mmol) and diethyl ether (18.7 mL) was added, via syringe, TMSCl (195 μL, 1.5 mmol) and the mixture was heated to reflux for 20 min, after which it was cooled to r.t., and stirred for an additional 20 minutes. Ethyl bromoacetate (1.41 mL, 12.7 mmol) was then added via syringe, and the mixture was heated at reflux with stirring for several hours, until all the Zn appeared to have reacted. The resulting yellow solution was then transferred to another round bottom flask via cannula, leaving behind any unreacted Zn. The remaining Zn was weighed, and the reaction re-scaled accordingly. Into the ethereal solution of the Reformatsky reagent at – 10 °C was added **84** (685 mg, 2.93 mmol) in diethyl ether (4 mL) via cannula and this was stirred (allowing the cooling bath to expire) until the starting material was consumed (36 hours), as determined by G.C. analysis. The reaction mixture was then diluted with diethyl ether (15 mL) and quenched by the addition of saturated aqueous NH_4Cl (15 mL) and water (10 mL). The organic layer was separated and the aqueous layer extracted with diethyl ether (15 mL). The combined organic extracts were washed with water (30 mL), brine (30 mL), dried over $MgSO_4$, then concentrated to give the crude product as a yellow oil. This was then purified by gradient column chromatography (1, 2, 4, 8, 15, 30 % EtOAc/ hexanes) to give 930 mg of the Reformatsky addition product as a ~50 : 1 ratio of *cis* : *trans* adducts (determined by G.C. analysis) in 83 % overall yield: R_f 0.42 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3522, 2951, 2869, 2829, 1732, 1716, 1456, 1372, 1334, 1190, 1126, 1054 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.29 (dd, J = 5.5, 5.5 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.27 (s, 6H), 3.20 (br s, 1H), 2.65 (d, J_{AB} = 15.5 Hz, 1H), 2.32 (d, J_{AB} = 15.5 Hz, 1H), 1.99 – 1.90 (m, 1H), 1.90 – 1.81 (m, 1H), 1.78 – 1.52 (m, 5H), 1.39 (m, 1H), 1.23 (t, J = 7.1 Hz, 3H), 1.14-1.05 (m, 1H), 0.98 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 104.9, 80.4, 60.6, 56.1, 52.7, 52.6, 44.4, 38.9, 38.6,

31.8, 31.2, 23.4, 21.1, 14.1; HRMS (ESY) calcd for $C_{15}H_{28}O_5Na$ (M+Na) 311.1834; found 311.1833.

To a stirred solution of the Reformatsky addition product (0.604 g, 2.61 mmol, 1 equiv) in CH_2Cl_2 (130 mL) at –10 °C was added BF_3•OEt_2 (332 μL, 2.61 mmol, 1 equiv) and the resulting mixture was stirred for an additional 10 min., at which time T.L.C. analysis showed the reaction to be complete. This was then quenched by the addition of Et_3N (3 mL) and water (50 mL), the aqueous phase was back-extracted with CH_2Cl_2 (50 mL). The combined organic extracts were washed with water (30 mL), brine (30 mL), dried over $MgSO_4$, then concentrated to give the crude product as a yellow oil. This was then purified by gradient column chromatography (5, 10, 15 % EtOAc / hexanes) to give 490 mg of product **89** (as a ~1 : 1 mixture of anomers, in an overall yield of 89%: **89 α:** R_f 0.66 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2950, 2867, 2831, 1732, 1455, 1371, 1342, 1319, 1204, 1156, 1125, 1050 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.57 (dd, J = 9.8, 2.6 Hz, 1H), 4.18 (dq, J = 10.8, 7.2 Hz, 1H), 4.06 (dq, J = 10.8, 7.1 Hz, 1H), 3.38 (s, 3H), 2.96 (d, J_{AB} = 13.3 Hz, 1H), 2.30 (d, J_{AB} = 13.3 Hz, 1H), 2.18 – 2.09 (m, 1H), 2.06 – 1.90 (m, 3H), 1.78 – 1.73 (m, 2H), 1.60 – 1.55 (m, 1H), 1.52 – 1.43 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H), 1.19-1.12 (m, 1H), 1.09 (ddd, J = 3.3, 3.3 Hz, 1H), 0.93 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 98.5, 84.3, 60.3, 55.9, 49.1, 40.9, 38.3, 34.1, 31.4, 26.0, 19.7, 19.2, 14.3; HRMS (ESY) calcd for $C_{14}H_{24}O_4Na$ (M+Na) 279.1572, found; 279.1573.

89 β: R_f 0.72 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2952, 2870, 1732, 1447, 1391, 1368, 1326, 1302, 1275, 1211, 1160, 1132, 1114 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.62 (dd, J= 4.2, 2.2 Hz, 1H), 4.09 (q, J=7.1 Hz, 2H), 3.34 (s, 3H), 2.94 (d, J_{AB}=15.9 Hz, 1H), 2.76 (d, J_{AB}=15.9 Hz, 1H), 2.07 – 2.86 (m, 4H), 1.85 – 1.77 (m, 2H), 1.51 – 1.40 (m, 3H), 1.23 (t, J=7.2 Hz, 3H), 1.16-1.08 (m, 1H), 0.94 (d, J=7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 99.7, 82.1, 60.0, 55.4, 48.8, 43.8, 38.5, 35.3, 31.6, 24.6, 19.4, 15.9, 14.2; HRMS (ESY) calcd for $C_{14}H_{24}O_4Na$ (M+Na) 279.1572; found 279.1571.

Vinyl ether of 89: R_f 0.78 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3057, 2954, 2872, 1733, 1368, 1328, 1291, 1235, 1209 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.26 (ddd, J =

6.2, 2.2, 1.5 Hz, 1H), 4.69 (ddd, J = 6.0, 6.0, 1.8 Hz, 1H), 4.11 (m, 2H), 2.68 (dd, J_{AB} = 13.3, 2.0 Hz, 1H), 2.37 (ddd, J = 12.5, 9.0, 1.5 Hz, 1H), 2.07 (ddd, J = 16.6, 5.0, 1.4 Hz, 1H), 2.06 (d, J_{AB} = 13.3 Hz, 1H), 1.94 (dddd, J = 13.6, 13.6, 13.6, 8.9 Hz, 1H), 1.71-1.63 (m, 2H), 1.57 – 1.44 (m, 2H), 1.33 (dddd, J = 13.8, 9.4, 7.0, 2.5 Hz, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.02 (d, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 142.9, 99.9, 81.7, 60.3, 50.7, 34.2, 33.9, 32.4, 28.3, 21.9, 19.6, 14.2; HRMS (ESY) calcd for $C_{13}H_{20}O_3Na$ (M+Na) 247.1305; found: m/z 247.1306; Anal calcd for $C_{13}H_{20}O_3$ C, 69.61; H, 8.99; found C, 69.21; H, 9.29.

Mixed thioacetal 90. To a pre-stirred (10 min) solution of **89** (0.49 g, 1.91 mmol, 1 equiv) and thiocresol (238 mg, 1.91 mmol, 1 equiv) in CH_2Cl_2 (96 mL) at –10 °C was added BF_3•OEt_2 (243 μL, 1.91 mmol) and the resulting mixture was stirred for an additional 7 min. (at which time TLC analysis showed the reaction to be complete) prior to being quenched by the addition of Et_3N (3 mL) and water (40 mL). The aqueous phase was then back-extracted with CH_2Cl_2 (40 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, then concentrated to give the crude product as a yellow oil dispersed in an unknown solid material (which is removed by dissolving the crude product in diethyl ether and filtering). The crude product was then purified by radial chromatography (4 mm plate, eluting with 1, 5, 25 % EtOAc / hexanes) to give 550 mg of **90** as a single anomer in 82.5 % yield, as well as dithioacetal **91** in 11 % yield.

Product 90: R_f 0.79 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2949, 2866, 1733, 1598, 1493, 1454, 1440, 1368, 1326, 1302, 1270, 1214, 1186, 1150, 1095 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 8.2 Hz, 2H), 7.06 (d, J = 8.2 Hz, 2H), 4.85 (m, J = 4.4, 2.0 Hz, 1H), 4.00 (dq, J = 10.9, 7.2 Hz, 1H), 3.89 (dq, J = 10.9, 7.2 Hz, 1H), 2.83 (d, J_{AB} = 13.7 Hz, 1H), 2.43 (d, J_{AB} = 13.7 Hz, 1H), 2.29 (s, 3H), 2.12 – 1.92 (m, 4H), 1.80 (m, 1H), 1.73, (m, 1H), 1.70 – 1.60 (m, 2H), 1.20 – 1.12 (m, 2H), 1.15 (t, J = 7.2 Hz, 3H), 0.91 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 137.4, 133.0, 130.0, 129.3, 85.1, 79.8, 60.3, 48.1, 39.5, 38.1, 33.9, 31.4, 26.2, 21.1, 20.8, 19.2, 14.2; HRMS (ESY) calcd for $C_{20}H_{28}O_3Na$ (M+Na) 371.1657; found 371.1658.

Carboxylic Acid 92: To a stirred solution of **90** (550 mg, 1.56 mmol, 1 equiv) in MeOH (2.6 mL) and THF (2.6 mL) at r.t. was added 2M LiOH (1.6 mL, 3.2 mmol, 2 equiv) and the reaction mixture was allowed to stir overnight at r.t.. This was then diluted with diethyl ether (20 mL) and water (20 mL) and the aqueous phase separated. The organic phase was back-extracted with water (20 mL) and the combined aqueous extracts were slowly acidified to pH ~3 with 0.5 N HCl (the exact volume was not measured). This was then diluted with EtOAc (40 mL) and the organic phase separated. The aqueous phase was back-extracted with EtOAc (20 mL) and the combined organic extracts were washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, then concentrated to give 497 mg of **92** as a pale yellow gum in 98 % yield: R_f 0.10 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3600 – 2400, 3020, 2949, 2866, 1707, 1492, 1439, 1411, 1375, 1303, 1240, 1150, 1093 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.4 – 10.6 (br s, 1H), 7.38 (d, J = 8.1 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 4.86 (dd, J = 10.4, 3.8 Hz, 1H), 2.95 (d, J_{AB} = 14.3 Hz, 1H), 2.40 (d, J_{AB} = 14.3 Hz, 1H), 2.31 (s, 3H), 2.13 – 1.95 (m, 4H), 1.84 - 1.74, (m, 2H), 1.72 – 1.61 (m, 2H), 1.22 – 1.16 (m, 2H), 0.93 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 137.8, 133.3, 129.4, 129.3, 85.1, 80.4, 48.4, 39.2, 38.0, 34.0, 31.2, 26.1, 21.2, 20.8, 19.2; HRMS (ESY) calcd for $C_{18}H_{24}O_3SNa$ (M+Na) 343.1344; found 343.1343.

Mixed Carbonic Anhydride of 92: To a stirred solution of **92** (138 mg, 0.43 mmol) in Et_2O (1.8 mL) with Et_3N (63 μL, 1.05 equiv) was added *i*BuOC(O)Cl (59 μL, 1.05 equiv) and the resulting mixture stirred at 0 °C for an additional 2h, at which time it was filtered. The filtrate was then concentrated and purified by radial chromatography to give 55 mg of the mixed carbonic anhydride in 29 % yield as an oil: R_f 0.76 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 2952, 2868, 1804, 1493, 1455, 1439, 1397, 1378, 1345, 1180 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 8.2 Hz, 2H), 7.06 (d, J = 8.2 Hz, 2H), 4.83 (m, J = 5.0 Hz, 1H), 4.02 (d, J = 6.7 Hz, 2H), 2.94 (d, J_{AB} = 14.3 Hz, 1H), 2.67 (d, J_{AB} = 14.3 Hz, 1H), 2.32 (s, 3H), 2.13 – 1.98 (m, 5H), 1.83 – 1.76 (m, 2H), 1.72 - 1.64 (m, 2H), 1.28 (ddd, J = 10.2, 4.2, 3.0 Hz, 1H), 1.21 (m, 1H), 0.97 (d, J = 6.7 Hz, 6H), 0.94 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 148.9, 137.5, 132.9, 129.9, 129.4, 84.7,

80.2, 75.5, 47.9, 39.1, 37.9, 34.0, 31.2, 27.6, 26.1, 21.1, 20.8, 19.2, 18.8; HRMS (ES) for $C_{23}H_{32}O_5SNa$ calcd 443.1868, found: m/z 443.1868.

Diazoketone 83: To a stirred solution of **92** (723 mg, 2.26 mmol) in CH_2Cl_2 (90 mL) at –15 °C was added 2,6-lutidine (316 μL, 2.71 mmol) and oxalyl chloride (237 μL, 0.93 mmol), followed by a catalytic amount (10 μL) of DMF, and the resulting mixture was stirred for 3 hours at this temperature. This was then condensed by rotary evaporation, the residue was dissolved in diethyl ether and filtered to give an ethereal solution of the corresponding acid chloride. This was then added via cannula into a freshly prepared ethereal solution of diazomethane (10 mmol) at –15 °C and allowed to stir overnight, while warming to r.t.. The reaction mixture was then concentrated under a stream of argon, dissolved in diethyl ether and filtered through a plug of silica, eluting with diethyl ether. This was then purified by radial chromatography (4 mm plate, eluting with 1, 5, 15 % EtOAc / Hexanes) to give 543 mg of **83** as a bright yellow crystalline solid, in an overall 69.9 % yield: R_f 0.55 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 3106, 2949, 2866, 2100, 1733, 1634, 1492, 1455, 1436, 1360, 1258, 1213, 1163 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 7.9 Hz, 2H), 4.83 (d, J = 10.8 Hz, 1H), 4.54 (s, 1H), 3.01 (d, J_{AB} = 15.0 Hz, 1H), 2.29 (s, 3H), 2.13 (m, 1H), 2.02 (m, 1H), 2.00 (d, J_{AB} = 14.8 Hz, 1H), 1.90 – 1.80 (m, 2H), 1.82 - 1.60 (m, 4H), 1.13 (ddd, J = 12.4, 9.0, 9.0 Hz, 1H), 1.03 (m, 1H), 0.90 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.4, 138.7, 135.0, 129.7, 129.0, 84.9, 81.2, 55.0, 49.9, 45.1, 36.7, 33.5, 31.1, 25.7, 21.1, 20.4, 18.8; HRMS (ES) for $C_{19}H_{24}N_2O_2SNa$ calcd 367.1451, found: m/z 367.1449; Anal calcd for $C_{19}H_{24}N_2O_2S$ C, 66.25; H, 7.02; N, 8.13; found C, 65.90; H, 7.41; N, 7.87.

Acid chloride of carboxylic acid 92: R_f 0.40 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 3019, 2949, 2866, 1812, 1738, 1708, 1651, 1492, 1454, 1439, 1399, 1377, 1301, 1264, 1212, 1180 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 8.2 Hz, 2H), 7.12 (d, J = 7.8 Hz, 2H), 4.80 (dd, J = 10.8, 3.4 Hz, 1H), 3.48 (d, J_{AB} = 15.4 Hz, 1H), 2.98 (d, J_{AB} = 15.5 Hz, 1H), 2.33 (s, 3H), 2.14 – 1.97 (m, 4H), 1.83 - 1.64, (m, 4H), 1.25 – 1.16 (m, 2H), 0.94 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 137.9, 133.3, 129.6, 129.4, 84.7, 80.7, 51.4, 48.2, 38.0, 33.9, 31.3, 26.0, 21.2, 20.9, 20.8, 19.1.

Oxygen-bridged, fused bicycle 82: To a solution of $Cu(hfacac)_2$ (73 mg, 0.147 mmol, 10 mol %) in CH_2Cl_2 (150 mL, 0.01 M) heated at reflux was added, via cannula, a solution of **83** (506 mg, 1.47 mmol) in CH_2Cl_2 (2 mL) and the resulting mixture stirred at reflux until **83** was consumed (45 min), as determined by T.L.C.. The reaction mixture was then cooled to r.t. and quenched by the addition of 0.5 M K_2CO_3 solution (80 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (80 mL). The combined organic extracts were washed with water (100 mL), brine (100 mL), dried over $MgSO_4$, concentrated then purified by radial chromatography (4 mm plate, eluting with 1, 5, 15 % EtOAc / Hexanes) to give 416 mg of **82** as a crystalline solid in 89.4 % yield: m.p.: 88 – 90 °C; R_f 0.74 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 3020, 2950, 2927, 2865, 1755, 1699, 1651, 1493, 1455, 1400, 1376, 1358, 1295, 1260 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 7.9 Hz, 2H), 4.24 (dd, J = 10.4, 3.8 Hz, 1H), 3.59 (ddd, J = 6.6, 4.9, 1.4 Hz, 1H), 2.70 (dd, J_{AB} = 13.5, 1.0 Hz, 1H), 2.38 (dd, J_{AB} = 13.5, 1.0 Hz, 1H), 2.31 (s, 3H), 2.11 (m, 1H), 2.04 – 1.90 (m, 4H), 1.85 (ddd, J = 14.6, 9.8, 6.8 Hz, 1H), 1.65 (ddd, J = 14.8, 9.9, 4.9 Hz, 1H), 1.44 (ddd, J = 14.1, 9.2, 4.0 Hz, 1H), 1.16 (m, 2H), 0.96 (d, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.4, 137.3, 132.3, 130.9, 129.8, 91.5, 83.1, 58.9, 51.6, 50.0, 38.5, 38.4, 32.4, 27.1, 23.9, 21.0, 18.6; HRMS (EI) calcd for $C_{19}H_{24}O_2S$ 316.1497; found 316.1506; Anal calcd for $C_{19}H_{24}O_2S$ C, 72.11; H, 7.64; found C, 71.91; H, 7.73.

Methyl adduct of bicycle 82: To a stirred solution of **82** (61 mg, 0.20 mmol) in THF (1.2 mL, 0.25 M) at 0 °C was added 3.0 M MeMgBr in THF (100 μL, 1.5 equiv) and the reaction was stirred for 1 h. whereupon TLC analysis showed the reaction to be near completion. Upon further stirring, no additional change was observed so the reaction mixture was quenched by addition of saturated aqueous NH_4Cl (20 mL) and water (10 mL). The organic layer was separated and the aqueous layer extracted with diethyl ether (20 mL). The combined organic extracts were washed with water (30 mL), brine (30 mL), dried over $MgSO_4$, then concentrated. This was then purified by radial chromatography (2 mm plate, eluting with 1, 5, 15 % EtOAc / hexanes) to give 45.5 mg of the methyl adduct (a single diastereomer) as a crystalline solid in 91 % yield, based on

recovered **82** (13.5 mg): m.p.: 106 - 108 °C; R_f 0.56 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 3320, 2949, 2927, 2867, 1492, 1439, 1375, 1307, 1274, 1247, 1201 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, J = 8.2 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 3.91 (d, J = 2.0 Hz, 1H), 3.73 (ddd, J = 3.0, 3.0, 2.2 Hz, 1H), 2.31 (s, 3H), 2.18 (d, J_{AB} = 13.2 Hz, 1H), 2.07 (d, J_{AB} = 13.2 Hz, 1H), 1.99 – 1.84 (m, 4H), 1.84 – 1.72 (m, 2H), 1.68 – 1.59 (m, 2H), 1.42 (s, 3H), 1.30 – 1.20 (m, 2H), 1.11 (ddd, J = 12.3, 8.8, 8.8 Hz, 1H), 0.93 (d, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.9, 132.5, 132.0, 129.6, 92.7, 89.1, 78.9, 58.8, 52.7, 50.1, 40.6, 39.2, 32.6, 31.4, 27.4, 24.6, 21.0, 18.8; HRMS (ES) calcd for $C_{20}H_{28}O_2SNa$ 355.1702, found 355.1701.

Ether-cleaved diol 81: A solution of LiDBB in THF was prepared.[58,59] To a stirred solution of the methyl adduct of **82** (72 mg, 0.22 mmol) in THF (1 mL, 0.25 M) at –78 °C, containing a few crystals of 1,10-phenanthroline, was added 2.4 M nBuLi in hexanes until the colour changed to red. Into this was then added a freshly prepared solution of LiDBB in THF (the exact volume was not measured) until the green colour persisted, indicating an excess of LiDBB. The reaction was then stirred for 2 hours at this temperature, during which time the colour changed from green to red, and after which TLC analysis showed the consumption of starting material. The reaction mixture was warmed to r.t., diluted with diethyl ether (10 mL) and quenched by the addition of saturated aqueous NH_4Cl (15 mL) and water (10 mL). The organic layer was separated and the aqueous layer extracted with diethyl ether (10 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, then concentrated. The crude product was then purified by column chromatography (1, 15, 30 % EtOAc / hexanes) to give 36 mg of **81** as a crystalline white solid in 79 % yield: R_f 0.32 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 3434, 3348, 3001, 2969, 2960, 2925, 2871, 1481, 1452, 1376, 1363, 1322, 1291, 1255, 1225, 1180 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.56 (m, 2H), 2.44 – 2.36 (m, 1H), 2.32 – 2.25 (m, 1H), 2.19 (d, J_{AB} = 15.3 Hz, 1H), 2.15 (d, J_{AB} = 15.3 Hz, 1H), 2.10 (ddd, J = 13.9, 10.4, 5.5 Hz, 1H), 1.90-1.73 (m, 2H), 1.67 (ddd, J = 11.3, 11.3, 4.1 Hz, 1H), 1.60-1.52 (m, 2H), 1.52 – 1.42 (m, 1H), 1.28 (s, 3H), 1.12 (dddd, J = 15.0, 12.5, 8.5, 6.7 Hz, 1H), 0.93 (t, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 127.9, 82.6, 73.2, 52.4, 50.2, 42.7, 39.1, 34.0, 30.8, 26.1,

24.4, 19.3; HRMS (ES) calcd for $C_{13}H_{22}O_2Na$ 233.1512; found 233.1512; Anal calcd for $C_{13}H_{22}O_2$ C, 74.24; H, 10.54; found C, 74.77; H, 10.15. The alcohol protons were not observed in the ^1H NMR spectrum.

Hemi-ketal 94': To a stirred solution of diol **81** (61 mg, 2.9 mmol, 1 equiv) in CH_2Cl_2 (6 mL) was added PCC (188 mg, 3 equiv) and this was stirred at r.t. for 2 hours. This was then filtered over Celite and passed through a plug of silica, eluting with ether to afford 30 mg **94'** as an oil in 50 % overall yield: R_f 0.13 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 3377, 2948, 2929, 2867, 1452, 1438, 1376, 1364, 1330, 1282, 1233, 1214, 1123, 1101 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.28 (m, 1H), 3.18 (s, 1H), 2.36 (d, J_{AB} = 17.7 Hz, 1H), 2.19 (m, 1H), 2.04 (m, 1H), 1.82 (ddd, J = 14.2, 9.2, 5.0 Hz, 1H), 1.74 (ddd, J = 14.0, 5.0, 5.0 Hz, 1H), 1.71 (s, 3H), 1.72-1.62 (m, 4H), 1.45 (m, 1H), 1.18 (dddd, J = 13.0, 11.2, 8.0, 5.4 Hz, 1H), 1.03 (dd, J = 10.7, 5.5 Hz, 1H), 0.94 (t, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.7, 123.7, 96.0, 84.7, 50.9, 38.9, 38.9, 35.3, 30.8, 29.2, 22.3, 20.6, 29.4; HRMS (ESY) calcd for $C_{13}H_{20}O_2Na$ (M+Na) 233.1148; found: m/z 233.1511.

Acetate 95: Into a stirred solution of the methyl adduct of **82** (205 mg, 0.61 mmol, 1 equiv) in CH_2Cl_2 (2.4 mL) at r.t. was added acetic anhydride (86 μL, 0.92 mmol, 1.5 equiv), triethylamine (120 μL) followed by DMAP (8 mg, 10 mol%) and the resulting mixture was stirred overnight, at which time TLC analysis indicated consumption of starting material. The reaction was diluted with hexanes (10 mL) and washed with 10 % HCl (5 mL), followed by brine (10 mL), and dried over anhydrous magnesium sulfate. This was then concentrated to give 185 mg of **95** (a single diastereomer) as a white crystalline solid in 81 % yield: m.p.: 67-69 °C; R_f 0.79 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 2949, 2866, 1741, 1492, 1441, 1370, 1300, 1241, 1151, 1103 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 7.8 Hz, 2H), 4.20 (s, 1H), 3.58 (m, J = 1.8 Hz, 1H), 2.52 (d, J_{AB} = 14.0 Hz, 1H), 2.35 (d, J_{AB} = 14.0 Hz, 1H), 2.32 (s, 3H), 2.00 (s, 3H), 2.02 – 1.94 (m, 2H), 1.93 - 1.83 (m, 4H), 1.73 (ddddd, J = 13.0, 10.1, 10.1, 6.5, 6.5 Hz, 1H), 1.64 (ddd, J = 13.6, 6.4, 6.4 Hz, 1H), 1.58 (s, 3H), 1.22 (ddd, J = 9.8, 9.8, 6.0 Hz, 1H), 1.11 (m, 1H), 0.94 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125

MHz, $CDCl_3$) δ 169.9, 137.0, 132.5, 131.9, 129.7, 92.8, 88.9, 85.3, 59.6, 51.8, 50.7, 41.1, 40.1, 33.0, 27.6, 26.6, 24.3, 21.8, 21.1, 18.6; HRMS (ESY) calcd for $C_{22}H_{30}O_3SNa$ (M+Na) 397.1813; found 397.1813.

Allyl ether 98: To a stirred solution of **81** (27 mg, 0.13 mmol, 1 equiv) in CH_2Cl_2 (0.6 mL) at 0 °C was added *p*-anisaldehyde (16 μL, 0.19 mmol, 1 equiv) followed by TMSOTf (1 μL, 5 mol%) and the reaction was allowed to warm to r.t.. Upon consumption of **81**, the reaction mixture was passed through a plug of silica, eluting with ethyl acetate to afford an unquantified amount of **98** as the sole product: R_f 0.90 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 3015, 2926, 2866, 2724, 1451, 1438, 1422, 1378, 1357, 1327, 1287, 1217, 1185 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.34 (m, 1H), 4.34 (s, 1H), 2.38 (d, J_{AB} = 17.8 Hz, 1H), 2.23 (ddd, J = 8.6, 8.6, 6.8Hz, 1H), 2.01 (dddd, J = 13.0, 9.0, 9.0, 6.8 Hz, 1H), 1.90 - 1.82 (m, 2H), 1.73 (d, J_{AB} = 17.8 Hz, 1H), 1.72 (s, 3H), 1.71-1.64 (m, 2H), 1.47 (m, 1H), 1.22 – 1.13 (m, 2H), 1.09 (dd, J = 9.4, 4.6 Hz, 1H), 0.96 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.7, 121.9, 79.4, 69.8, 51.9, 39.6, 39.4, 35.4, 30.9, 22.8, 22.7, 19.5, 17.0; HRMS (EI) calcd for $C_{13}H_{20}O_0$ 192.1514; found 192.1513.

Dioxolane 99: A solution of **82** (270 mg, 0.84 mmol) in CH_2Cl_2 (5 mL) was cooled to 0 °C and to this bis(trimethylsiloxy)ethane (420 μL, 1.68 mmol) was added, followed by trimethylsilyl trifluoromethanesulfonate (9 μL, 5 mol%) and the resulting mixture was stirred overnight and allowed to slowly warm to r.t. as the cooling bath expired. The reaction was diluted with CH_2Cl_2 (10 mL) and quenched by the addition of pyridine (1 mL), then further diluted with a saturated sodium bicarbonate solution (15 mL). The inorganic layer was separated and washed with 15 mL of CH_2Cl_2. The combined organic extracts were washed with water (20 mL) then brine (20 mL), dried over anhydrous magnesium sulfate and concentrated. The crude product was then purified by column chromatography (silica gel; 5, 10, 25% EtOAc / hexanes) to afford 285 mg of **99** in 93% yield: R_f 0.76 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 2948, 2866, 1491, 1455, 1398, 1374, 1321, 1275, 1210 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 8.2 Hz, 2H), 4.11 (s, 1H), 3.94 (ddd, J = 8.0, 6.5, 4.8 Hz, 1H), 3.85 (ddd, J =

7.2, 7.2, 7.2 Hz, 1H), 3.78 (ddd, J = 6.9, 6.9, 4.9 Hz, 1H), 3.63 (ddd, J = 7.2, 7.2, 7.2 Hz, 1H), 3.51 (m, 1H), 2.36 (d, J_{AB} = 14.1 Hz, 1H), 2.32 (s, 3H), 2.28 (d, J_{AB} = 14.1 Hz, 1H), 2.08 – 1.98 (m, 1H), 1.97 – 1.85 (m, 5H), 1.82 (m, J = 9.6, 6.4 Hz, 1H), 1.68 – 1.59 (m, 1H), 1.23 (m, J = 7.7, 5.2 Hz, 1H), 1.16 – 1.07 (m, 1H), 0.94 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.0, 132.7 (2C), 131.8, 129.6, 92.5, 86.1, 65.2, 64.0, 59.1, 50.7, 49.4, 40.3, 39.3, 32.6, 27.4, 24.3, 21.1, 18.9; HRMS (EI) calcd for $C_{21}H_{28}O_3S$ 360.1759; found 360.1760.

Alcohol 100: A solution of LiDBB in THF was prepared. [58,59] To a stirred solution of **99** (35 mg, 0.097 mmol) in THF (0.4 mL, 0.25 M) at –78 °C, containing a few crystals of 1,10-phenanthroline, was added 2.4 M nBuLi in hexanes until the colour changed to red. Into this was then added a freshly prepared solution of LiDBB in THF (the exact volume is not measured) until the green colour persisted, indicating an excess of LiDBB. The reaction was then stirred for 16 hours as the cooling bath expired, and after which TLC analysis showed the consumption of starting material. The reaction mixture was diluted with Et_2O (10 mL) and quenched with saturated aqueous NH_4Cl (15 mL) and water (10 mL). The organic layer was separated and the aqueous layer extracted with Et_2O (10 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, then concentrated. The crude product was then purified by column chromatography (silica gel; 1, 15, 30 % EtOAc / hexanes) to give 15 mg of **100** in 65 % yield, as well as a small, unquantified amount of starting material **99**: R_f 0.44 (30% EtOAc/hexanes); IR (CH_2Cl_2 cast) 3508, 3020, 2949, 1461, 1393, 1376, 1276, 1186, 1119 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (ddd, J = 11.4, 9.8, 7.8 Hz, 1H), 5.56 (dd, J = 11.4, 1.2 Hz, 1H), 3.97 (m, 1H), 3.91 – 3.85 (m, 3H), 3.49 (s, 1H), 2.92 (ddddd, J = 12.8, 12.8, 8.6, 8.6, 1.2 Hz, 1H), 2.21 (d, J_{AB} = 14.4 Hz, 1H), 2.05 9M, 1H), 2.00 (d, J_{AB} = 14.4 Hz, 1H), 1.85 – 1.69 (m, 4H), 1.62 (m, 2H), 1.46 (m, 1H), 1.10 (m, 1H), 0.92 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.2, 132.6, 109.3, 81.1, 64.6, 63.1, 51.7, 50.9, 44.8, 41.2, 32.5, 27.1, 23.8, 19.0; HRMS (EI) calcd for $C_{14}H_{22}O_3$ 238.1569; found 238.1571.

Dimethylacetal 101: To a stirred solution of **61** (100 mg, 0.55 mmol, 1 equiv) in dry methanol (1.1 mL) was added trimethyl orthoformate (90 mL, 0.82 mmol. 1.5 equiv) and *p*TsOH (10 mg, 10 mol%) and the reaction stirred until T.L.C. analysis indicated consumption of **61**. The complex mixture of products was immediately purified by column chromatography without workup of the reaction mixture. From this complex mixture, a 12 mg sample of **101** was isolated, as well as 45 mg of other products. R_f 0.66 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 2955, 2871, 2829, 1740, 1456, 1388, 1186, 1155, 1109 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.83 (s, 1H), 3.47 (s, 3H), 3.43 (s, 3H), 2.34 – 2.25 (m, 1H), 2.10 – 1.99 (m, 2H), 1.76 – 1.49 (m, 3H), 1.40 (m, 1H), 1.24 (m, 1H), 0.99 (d, J = 6.4 Hz, 3H), 0.96 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.6, 114.0, 58.4, 58.2, 52.8, 39.5 39.3, 37.1, 35.7, 29.2, 22.5, 21.9, 19.3; HRMS (EI) calcd for $C_{13}H_{24}O_3$ 228.1726; found 228.1725.

Dithioacetal of 61: To a stirred solution of **61** (135 mg, 0.68 mmol, 1 equiv) and HSTol (170 mg, 1.36 mmol, 2 equiv) in CH_2Cl_2 (20 mL) was added BF_3OEt_2 (86 μL, 1 equiv). The reaction was stirred for an additional 10 min. at which time it was quenched by the addition of Et_3N (0.5 mL) and water (20 mL). The organic layer was separated and washed again with water (20 mL). The aqueous extracts were washed with CH_2Cl_2 (20 mL), then the combined organic extracts were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, then concentrated. The crude product was then purified by column chromatography (silica gel; 1, 15, 30 % EtOAc / hexanes) to give 210 mg of the dithioacetal in 76 % yield: R_f 0.74 (30% EtOAc / hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.16 (m, 4H), 7.01 (m, 4H), 4.23 (s, 1H), 2.34 (m, 1H), 2.30 (s, 6H), 2.17 – 2.04 (m, 2H), 1.95 (dd, J = 13.9, 6.4 Hz, 1H), 1.80 (m, 1H), 1.70 (dd, J = 14.0, 2.4 Hz, 1H), 1.65 (m, 1H), 1.46 (m, 1H), 1.19 (d, J = 6.4 Hz, 3H), 1.17 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.4, 137.5, 137.4, 133.5, 133.4, 132.8, 132.6, 129.5 (2C), 114.7, 77.2, 53.4, 41.8, 39.4, 38.2, 37.2, 31.6, 29.2, 26.1, 24.9, 22.6, 21.1, 21.0, 19.5, 14.1.

Bromomethyl ethyl acrylate 112:[67] Alcohol **111** (1.0 g, 7.7 mmol, 1 equiv) was stirred in Et_2O (8 mL) at -10 °C. To this was added PBr_3 (333 μL, 0.46 equiv) dropwise over ~10 minutes. The resulting solution was warmed to r.t. with stirring over a period of 3

hours. The reaction was quenched by the addition of water (8 mL), the layers were separated and to aqueous layer extracted three times with hexanes (10 mL). The combined organic extracts were pre-dried with brine (20 mL) and dried over $MgSO_4$ and concentrated to give 1.15 g of **102** as a clear, colourless oil in 77 % yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.34 (s, 1H), 5.95 (s, 1H), 4.37 (q, J = 6.4 Hz, 2H), 4.20 (s, 2H), 1.33 (t, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 137.6, 128.9, 61.3, 29.4, 14,1.

Alkylation Product 113: To a 50 mL round bottom flask was added sodium hydride (60 % dispersion in oil ; 185 mg, 4.6 mmol) which was rinsed with 5 mL of hexanes. The hexanes was decanted, and the flask charged with 10 mL of THF. To this stirred suspension was added a solution of **52** (0.60 g, 3.8 mmol) in THF (5 mL) slowly over a period of 10 minutes, and the resulting mixture stirred at room temperature for a further 15 minutes, until all the sodium hydride was reacted. To this was then added a solution of **112** (1.11 g, 5.76 mmol) in THF (4 mL). A white precipitate formed immediately upon addition of **112**, and T.L.C. analysis of the reaction mixture after 30 min. showed complete consumption of **52**. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (15 mL). The organic layer was separated and the aqueous layer extracted twice with Et_2O (15 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, then concentrated to give the crude product as a yellow oil. This was then purified by gradient column chromatography (2, 4, 8, 16, 25 % EtOAc / hexanes) to give 875 mg of **113** as a 7.9 : 1 ratio of isomers in 86 % yield: R_f 0.45 (30% EtOAc / hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.25 (m, 1H), 5.63 (m, 1H), 4.20 (m, J = 7.0 Hz, 2H), 3.69 (s, 3H), 3.09 (d, J_{AB} = 14.1 Hz, 1H), 2.88 (d, J_{AB} = 14.2 Hz, 1H), 2.52 (dd, J = 18.6, 8.5 Hz, 1H), 2.14 (m, 1H), 2.10 – 197 (m, 2H), 1.77 (ddd, J = 11.5, 7.9, 7.9 Hz, 3H), 1.30 (t, J = 7.1 Hz, 1H), 1.05 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.5, 170.7, 167.5, 136.4, 129.8, 64.3, 70.0, 51.9, 39.1, 39.0, 31.4, 28.1, 15.7, 14.1;

Transesterification product 116: To a stirred solution of **52** (100 mg, 0.62 mmol, 1 equiv) and **115** (145 mg, 0.92 mmol, 1.5 equiv) in toluene (2 mL) was added DMAP (23 mg, 30 mol%) and the resulting mixture heated at reflux for 4 days. The reaction mixture

was then cooled and quenched by the addition of saturated aqueous NH_4Cl. The organic layer was separated and the aqueous layer extracted three times with Et_2O (10 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, then concentrated to give the crude product as a yellow oil. This was then purified by gradient column chromatography (2.5, 5, 10, 20 % EtOAc / hexanes) to give 124 mg of **116** in 69 % yield as an oil: R_f 0.42 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 2975, 2932, 2876, 1757, 1730, 1330, 1294, 1120, 1061 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.40 (m, 1H), 5.33 (m, 1H), 4.90 (s, 1H), 4.77 (d, J = 13.9 Hz, 1H), 4.69 (d, J = 13.9 Hz, 1H), 3.63 (m, 2H), 3.50 (m, 2H), 2.82 (d, J = 11.3 Hz, 1H), 2.63 (m, 1H), 2.44 (dd, J = 18.6, 8.4 Hz, 1H), 2.33 (ddd, J = 18.8, 11.4, 8.6 Hz, 1H), 2.21 (dddd, J = 12.6, 6.2, 6.2, 1.8 Hz, 1H), 1.49 (dddd, J = 12.6, 11.3, 11.3, 8.3 Hz, 1H), 1.21 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.5, 168.7, 140.7, 115.1, 101.2, 64.0, 63.0, 61.9, 61.8, 38.7, 36.4, 29.4, 19.3, 15.1 (2C); HRMS (EI) calcd for $C_{15}H_{24}O_5$ 284.16238; found 284.16179.

***t*-Butyl Ester 121:** The exact procedure of Marx and Norman[38] was followed, employing tBuOH instead of MeOH, to afford 12.9 g of **121** in 47 % yield as an inseparable 1 : 1 mixture of diasteromers: R_f 0.62 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 2958, 2872, 1726, 1456, 1391, 1366, 1294, 1166, 1140 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.28 (d, J = 8.0 Hz, 1H), 2.83 (d, J = 5.6 Hz, 2H), 2.44 (dd, J = 16.5, 8.6 Hz, 1H), 2.36 (m, 1H), 2.30 – 2.12 (m, 4H), 1.95 (m, 1H), 1.75 (m, 2H), 1.65 – 1.62 (4s, 12H), 1.44 (s, 18 H), 1.28 – 1.17 (m, 2H), 1.07 (d, J = 7.2 Hz, 3H), 1.04 (d, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 173.5, 135.7, 134.8, 125.3, 125.1, 79.9, 79.7, 56.8, 53.7, 40.8, 39.0, 33.8, 32.8, 30.5, 30.3, 28.2, 28.0, 21.4, 21.2, 21.2, 21.0, 19.7, 15.7; HRMS (EI) calcd for $C_{14}H_{24}O_2$ 224.17763; found 224.17752.

***t*-Butyl β-Keto Ester 120:** A solution of **121** (1g, 4.5 mmol) in EtOAc (40 mL) was cooled to -78 °C and ozonized until a blue colour persisted. At this time oxygen was continued bubbling through the flask until the colour dissipated, and then DMS (6 mL) was added and the reaction stirred over night as the cooling bath expired. The mixture was then concentrated, redissolved in Et_2O (30 mL) and washed successively with 0.5M HCl (10 mL), water (20 mL). The aqueous washes were extracted with ether, and then

the combined organic extracts were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, then concentrated. This was then purified by gradient column chromatography (silica gel; 5, 10, 20 % EtOAc / hexanes) to give 884 mg of **120** in 87 % yield as a single diastereomer: R_f 0.59 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 2962, 2932, 2873, 1754, 1720, 1457, 1367, 1164, 1127 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.65 (d, J = 11.6 Hz, 1H), 2.54 (m, 1H), 2.39 (dd, J = 19.6, 7.3 Hz, 1H), 2.31 (ddd, J = 19.9, 11.3, 7.4 Hz, 1H), 2.18 (dddd, J = 10.6, 8.2, 7.1, 1.9 Hz, 1H), 1.50 – 1.40 (m, 1H), 1.47 (m, 9H), 1.18 (d, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.3, 168.5, 81.6, 64.1, 38.7, 36.4, 29.3, 28.1, 19.3; HRMS (EI) calcd for $C_{11}H_{18}O_3$ 198.12560; found 198.12557.

Carboxylic Acid 119: To a stirred solution of **120** (500 mg, 2.2 mmol, 1 equiv) in CH_2Cl_2 (20 mL) was added CF_3CO_2H in 1 mL portions at a rate of one every hour until **120** was consumed, as determined by T.L.C. analysis. The reaction mixture was then concentrated, and placed under hi-vac until a constant weight was obtained, which afforded 319 mg of **119** as an oil (which solidified upon refrigeration) in 92 % yield: R_f 0.15 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 3400 – 2300, 2962, 2875, 1754, 1459, 1405, 1156, 1133 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11 – 9 (br. s, 1H), 2.79 (d, J = 11.6 Hz, 1H), 2.59 (m, 1H), 2.49 (dd, J = 19.1, 9.4 Hz, 1H), 2.36 (ddd, J = 19.1, 11.1, 8.7 Hz, 1H), 2.22 (dddd, J = 12.8, 8.1, 6.2, 1.6 Hz, 1H), 1.50 (dddd, J = 12.8, 11.6, 11.6, 8.2 Hz, 1H), 1.26 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.3, 173.6, 62.3, 38.7, 36.2, 29.2, 19.4; HRMS (EI) calcd for $C_7H_{10}O_3$ 142.0630; found 142.0636.

TBDPS-protected β-keto ester 124: To a stirred solution of **52** (50 mg, 0.32 mmol, 1 equiv) in $PhCH_3$ (2 mL) was added **123** (104 mg, 1 equiv) and transesterification catalyst **117** (32 mg, 10 mol%). This was heated at reflux overnight, after which the reaction mixture was concentrated and purified directly by gradient column chromatography (silica gel; 1, 2, 5, 10, 18 % EtOAc / hexanes) to give 72 mg of **124** in 50 % yield: R_f 0.62 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 2959, 2932, 2858, 1757, 1730, 1462, 1428, 1363, 1188, 1113 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (m, 4H), 7.41 (m, 6H), 5.34 (s, 1H), 5.21 (s, 1H), 4.72 (s, 2H), 4.22 (s, 2H), 2.75 (d, J = 11.4 Hz, 1H), 2.55 (m,

1H), 2.41 (dd, J = 18.7, 8.6 Hz, 1H), 2.29 (ddd, J = 18.7, 11.4, 8.7 Hz, 1H), 2.17 (m, 1H), 1.46 (dddd, J = 11.3, 11.3, 11.3, 8.4 Hz, 1H), 1.14 (d, J = 6.2 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.4, 168.8, 142.4, 135.5, 133.4, 129.7, 129.7, 127.7, 113.0, 65.3, 64.4, 63.0, 38.7, 36.4, 29.4, 26.8, 19.3 (2C); HRMS (EI) calcd for $C_{23}H_{25}O_4Si$ (M-*t*Bu) 393.15222; found 393.15277.

TES-protected Alcohol 125: To a stirred solution of **111** (4.75 g, 36.5 mmol, 1 equiv) in CH_2Cl_2 (36.5 mL) at 0 °C was added Et_3N (5.6 mL, 40.1 mmol, 1.1 equiv) followed by TESOTf (9.08 mL, 40.1 mmol, 1.1 equiv) and the reaction stirred for 30 min., at which time T.L.C. analysis of the reaction mixture indicated consumption of **111**. The reaction was quenched by the addition of a saturated aqueous $NaHCO_3$ solution. The layers were separated and the organic layer concentrated. The residue was redissolved in Et_2O (30 mL) and this was washed successilvely with water (30 mL), brine (30 mL). The organic layer was dried over $MgSO_4$ and concentrated to give 8.89 g of TES protected **111** as a pure oil in quantitative yield: R_f 0.24 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 2957, 2913, 2877, 1715, 1641, 1461, 1306, 1270, 1176, 1096 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (q, J = 1.9 Hz, 1H), 5.90 (q, J = 2.1 Hz, 1H), 4.36 (t, J = 2.0 Hz, 2H), 4.20 (q, J = 7.1 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.8 Hz, 9H), 0.63 (q, J = 7.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 139.9, 123.6, 61.1, 60.5, 14.2, 6.7, 4.4; HRMS (EI) calcd for $C_{10}H_{19}O_3Si$ (M-Et) 215.1104; found 215.1108.

To a stirred solution of the TES-protected ester **111** (2g, 8.18 mmol, 1 equiv) at -78 °C in CH_2Cl_2 (40 mL) was added a 1.0 M solution of Dibal-H (20.5 mL, 2.5 equiv) and the reaction mixture was allowed to warm to r.t. over several hours. The reaction was again cooled to -78 °C and quenched by the addition of water (10 mL). This was allowed to warm to r.t., at which resulted in an emulsion. Successive dilutions with water and Et_2O allowed for the layers to be separated. The organic layer was washed with water (30 mL), then brine (30 mL), subsequently dried over $MgSO_4$ and concentrated to afford 875 mg **125** in 53 % yield. R_f 0.18 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 3359, 2956, 2913, 2877, 1458, 1416, 1240, 1112, cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11 (s, 1H), 5.09 (s, 1H), 4.25 (s, 2H), 4.18 (s, 2H), 0.97 (t, J = 7.9 Hz, 9H), 0.63 (q, J = 7.9 Hz, 6H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 120.1, 111.3, 64.9, 64.8, 6.8, 4.4; HRMS (EI) calcd for $C_8H_{17}O_2Si$ (M-Et) 173.0998; found 173.0992. The alcohol proton was not observed in the ^1H NMR spectrum.

TES-protected β-keto ester 126: To a stirred solution of **119** (517 mg, 3.63 mmol, 1 equiv) in CH_2Cl_2 (7.5 mL) was added **125** (882 mg, 4.36 mmol, 1.2 equiv) and the mixture was cooled to 0 °C. To this was added DMAP (22 mg, 5 mol%) followed by DCC (825 mg, 4.0 mmol 1.1 equiv) and the reaction was stirred for an additional 10 minutes, at which time T.L.C. analysis indicated the consumption of **119**. The reaction mixture was then filtered, concentrated and purified directly by gradient column chromatography (silica gel; 1, 2, 4, 8, 16 % EtOAc / hexanes) to give 635 mg of **126** in 53 % yield: R_f 0.57 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 2957, 2912, 2876, 1757, 1730, 1460, 1409, 1331, 1189, 1121 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.25 (d, J = 0.7 Hz, 1H), 5.16 (d, J = 1.1 Hz, 1H), 4.70 (d, J = 13.1 Hz, 1H), 4.66 (d, J = 13.1 Hz, 1H), 4.19 (d, J = 14.7 Hz, 1H), 4.16 (d, J = 14.7 Hz, 1H), 2.78 (d, J = 11.2 Hz, 1H), 2.59 (m, 1H), 2.41 (dd, J = 18.2, 8.1 Hz, 1H), 2.32 (dd, J = 11.5, 8.6 Hz, 1H), 2.19 (dddd, J = 12.7, 8.2, 6.2, 1.6 Hz, 1H), 1.47 (m, 1H), 1.18 (d, J = 6.5 Hz, 3H), 0.95 (t, J = 8.0 Hz, 9H), 0.60 (q, J = 8.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.4, 168.8, 142.9, 113.0, 65.3, 63.4, 63.0, 38.7, 36.4, 29.3, 19.2, 6.7, 4.4; HRMS (EI) calcd for $C_{15}H_{25}O_4Si$ (M-Et) 297.15308; found 397.15222.

Diethyl acetal 109: Into a flask containing **116** (155 mg, 0.55 mmol, 1 equiv) and PhH (2 mL) was added $Pd(PPh_3)_4$ (15 mg, 2.5 mol%) and the reaction mixture was stirred for 16 hours at r.t.. The reaction mixture was then concentrated and purified directly by gradient column chromatography (silica gel; 2, 5, 10, 25 % EtOAc / hexanes) to give 118 mg of **109** in 90 % yield: R_f 0.54 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 2956, 2930, 2857, 1741, 1472, 1461, 1428, 1407, 1378, 1157, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.25 (s, 1H), 5.02 (s, 1H), 4.73 (s, 1H), 3.62 – 3.56 (m, 2H), 3.49 – 3.42 (m, 2H), 2.44 (dd, J = 15.6, 5.3 Hz, 1H), 2.32 (m, 1H), 2.20 (dd, J = 15.6, 5.0 Hz, 1H), 2.15 – 2.05 (m, 2H), 1.97 – 1.92 (m, 2H), 1.47 – 1.37 (m, 1H), 1.21 (t, J = 7.0 Hz, 3H), 1.20 (t, J = 7.0 Hz, 3H), 1.13 (d, J = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.4, 143.9,

114.4, 103.4, 61.9, 61.6, 55.0, 37.5, 37.4, 30.0, 29.4, 19.9, 15.2, 15.1; HRMS (EI) calcd for $C_{14}H_{24}O_3$ 240.17255; found 240.17266.

TBDPS Adduct 127: Into a flask containing **124** (433 mg, 0.96 mmol, 1 equiv) and PhH (10 mL) was added $Pd(PPh_3)_4$ (111 mg, 2.5 mol%) and the reaction mixture was stirred for 16 hours at r.t.. The reaction mixture was then concentrated and purified directly by gradient column chromatography (silica gel; 2, 5, 10, 25 % EtOAc / hexanes) to give 287 mg of **127** in 74 % yield: R_f 0.54 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 2975, 2930, 2874, 1741, 1458, 1409, 1378, 1158, 1118 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.45 – 7.36 (m, 6H), 5.26 (m, 1H), 4.91 (d, J = 1.3 Hz, 1H), 4.12 (d, J = 14.5 Hz, 1H), 4.02 (d, J = 14.4 Hz, 1H), 2.42 (dd, J = 14.7, 5.2 Hz, 1H), 2.27 (m, 1H), 2.16 (dd, J = 15.0, 7.0 Hz, 1H), 2.05 – 1.92 (m, 2H), 1.83 – 1.67 (m, 2H), 1.34 (m, 1H), 1.08 (s, 9H), 1.06 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.2, 145.7, 135.6, 135.5, 133.6, 133.5, 129.7, 129.6, 127.7, 110.7, 66.2, 54.8, 37.5, 37.2, 31.9, 29.4, 26.9 (2C), 19.8, 19.3; HRMS (EI) calcd for $C_{22}H_{25}O_2Si$ (M-*t*Bu) 349.1624; found 349.1627.

TES Adduct 128: Into a flask containing **126** (250 mg, 0.77 mmol, 1 equiv) and PhH (2.6 mL) was added $Pd(PPh_3)_4$ (46 mg, 2.5 mol%) and the reaction mixture was stirred for 16 hours at r.t.. The reaction mixture was then concentrated and purified directly by gradient column chromatography (silica gel; 2, 5, 10, 25 % EtOAc / hexanes) to give 130 mg of **128** in 60 % yield: R_f 0.60 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 2955, 2912, 2876, 1742, 1461, 1411, 1378, 1157, 1106 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.25 (s, 1H), 5.02 (m, 1H), 4.86 (m, 1H), 4.08 (ddd, J = 14.4, 1.7, 1.3 Hz, 1H), 4.01 (ddd, J = 14.3, 1.7, 1.3 Hz, 1H), 2.44 (ddd, J = 14.2, 5.5, 0.6 Hz, 1H), 2.37 – 2.29 (m, 1H), 2.17 (dd, J = 14.9, 6.7 Hz, 1H), 2.13 – 2.06 (m, 2H), 1.95 – 1.86 (m, 1H), 1.81 (dddd, J = 10.5, 7.4, 5.5, 1.4 Hz, 1H), 1.41 (m, 1H), 1.13 (d, J = 6.4 Hz, 3H), (t, J = 8.0 Hz, 9H), 0.60 (q, J = 8.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.4, 146.1, 110.6, 65.4, 55.0, 37.6, 37.3, 31.8, 29.4, 19.8, 6.7, 4.4; HRMS (EI) calcd for $C_{14}H_{25}O_2Si$ (M-Et) 253.1624; found 253.1626.

Reformatsky Adduct 131: Wilkinson's catalyst, $(PPh_3)_3RhCl$, (11 mg, 2.5 mol%) was stirred in THF (3 mL) at r.t., and to this was added ethyl bromoacetate (80 μL, 1.5 equiv) followed by a solution of **109** (114 mg, 0.47 mmol, 1 equiv) in THF (2 mL). Subsequently, a 1.0 M solution of $ZnEt_2$ was added (1.04 mL, 2.2 equiv) and the reaction was stirred at r.t. until deemed complete by T.L.C. analysis. The reaction was found to have stalled after 24 hours, so an additional portion of catalyst (11 mg, 2.5 mol%) and $ZnEt_2$ (1.04 mL) were added, and the reaction stirred for an additional 24 hours, at which time it was quenched by the addition of saturated aqueous NH_4Cl. The layers were separated, and the aqueous layer was extracted twice with Et_2O (10 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, then concentrated. This was then purified by gradient column chromatography (silica gel; 2, 5, 10, 25 % EtOAc / hexanes) to give 70 mg of **131** as an inseparable mixture of diastereomers in a 3.4 : 1 ratio in 52 % yield, based on the recovery of **99** (15 mg). The major isomer: R_f 0.55 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 3518, 2976, 2953, 2871, 1717, 1444, 1373, 1188, 1118 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.23 (d, J = 1.2 Hz, 1H), 5.10 (s, 1H), 4.76 (s, 1H), 4.16 (m, 2H), 3.70 – 3.55 (m, 2H), 3.53 – 3.43 (m, 2H), 3.40 (s, 1H), 2.79 (d, J = 15.3 Hz, 1H), 2.35 (d, J = 15.4 Hz, 1H), 2.14 (dd, J = 16.2, 5.7 Hz, 1H), 1.97 (ddd, J = 12.6, 8.6, 6.6 Hz, 1H), 1.92 – 1.75 (m, 3H), 1.45 (m, 1H), 1.30 – 1.20 (m, 9H), 1.15 (m, 1H), 1.00 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 145.3, 114.7, 103.8, 80.5, 62.0, 61.8, 60.4, 54.3, 44.7, 38.8, 38.5, 31.0, 29.3, 20.3, 15.1 (2C), 14.2; HRMS (EI) calcd for $C_{18}H_{32}O_5$ 328.2250; found 328.2233. The alcohol proton was not observed in the ^1H NMR spectrum.

Allyl Alcohol 133: To a solution of **127** (29 mg, 0.7 mmol, 1equiv) in THF (1 mL) that was stirred at r.t. was added a 0.01 M solution of TBAF in THF (80 µL, 1 equiv) and the reaction was stirred for four hours at which time T.L.C. analysis of the reaction mixture indicated consumption of **127**. The reaction mixture was concentrated and purified directly by gradient column chromatography (silica gel; 2, 10, 2 x 20, 50 % EtOAc / hexanes) to give 8.4 mg of **133** in 70 % yield: R_f 0.16 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 3434 (br), 2954, 2867, 1738, 1460, 1408 1378, 1159 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.05 (q, J = 1.4 Hz, 1H), 4.89 (m, 1H), 4.01 (d, J_{AB} = 13.9 Hz, 1H), 3.98

(d, J_{AB} = 13.8 Hz, 1H), 2.43 – 2.33 (m, 3H), 2.19 – 2.08 (m, 2H), 1.93 – 1.81 (m, 2H), 1.44 (m, 1H), 1.16 (d, J = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 221.7, 146.7, 112.5, 65.8, 55.8, 37.6, 37.2, 31.0, 29.4, 19.4; HRMS (EI) calcd for $C_{10}H_{16}O_2$ 168.1150; found 168.1148. The alcohol proton was not observed in the ^{1}H NMR spectrum.

Reformatsky Adduct 134: Wilkinson's catalyst, $(PPh_3)_3RhCl$, (27 mg, 2.5 mol%) was stirred in THF (1 mL) at r.t., and to this was added ethyl bromoacetate (132 μL, 4 equiv) followed by a solution of **133** (50 mg, 0.30 mmol, 1 equiv) in THF (2 mL). Subsequently, a 1M solution of $ZnEt_2$ was added (1.8 mL, 6 equiv) and the reaction was stirred at r.t. until deemed complete by T.L.C. analysis. The reaction was found to be complete after 24 hours, at which time it was diluted in Et_2O (10 mL) and quenched by the addition of saturated aqueous NH_4Cl. The layers were separated, and the aqueous layer was extracted twice with Et_2O (10 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, then concentrated. This was then purified by gradient column chromatography (silica gel; 2, 30, 50 % EtOAc / hexanes) to give 27 mg of **134** in a 2 : 1 ratio of inseparable disatereomers in 39 % yield. The major isomer: R_f 0.08, 0.06 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 3432, 2951, 2869, 1733, 1457, 1378, 1189 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 (br s, 1H), 4.96 (s, 1H), 4.15 (m, 2H), 4.09 (s, 2H), 2.90 – 2.60 (br s, 2H), 2.77 (d, J_{AB} = 15.6 Hz, 1H), 2.37 (dd, J = 14.7, 7.5 Hz, 1H), 2.35 (d, J_{AB} = 15.6 Hz, 1H), 2.12 (dd, J = 14.8, 6.4 Hz, 1H), 2.01 - 1.94 (m, 1H), 1.91 – 1.84 (m, 1H), 1.82 – 1.73 (m, 2H), 1.30 (ddd, J = 9.3, 6.8, 6.8 Hz, 1H), 1.26 (t, J = 7.1 Hz, 3H), 1.13 (dddd, J = 12.4, 8.7, 7.3, 6.2 Hz, 1H), 0.98 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 148.2, 111.3, 80.5, 66.1, 60.6, 53.9, 44.4, 38.9, 38.9, 31.5, 30.9, 20.4, 14.1; HRMS (EI) calcd for $C_{14}H_{24}O_4$ 256.1675; found 256.1672.

Reformatsky Adduct 135: Wilkinson's catalyst, $(PPh_3)_3RhCl$, (40 mg, 10 mol%) was stirred in THF (1 mL) at r.t., and to this was added ethyl bromoacetate (188 μL, 4 equiv) followed by a solution of **128** (120 mg, 0.42 mmol, 1 equiv) in THF (3 mL). Subsequently, a 1M solution of $ZnEt_2$ was added (2.5 mL, 6 equiv) and the reaction was stirred at r.t. until deemed complete bt T.L.C. analysis. The reaction appeared to be

complete after 24 hours, at which time it was diluted in Et_2O (10 mL) and quenched by the addition of saturated aqueous NH_4Cl. The layers were separated, and the aqueous layer was extracted twice with Et_2O (10 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, then concentrated. This was then purified by gradient column chromatography (1, 2, 4, 8, 16 % EtOAc / hexanes) to give 92 mg of **135** as an inseparable mixture in a 3.9 : 1 ratio in 64 % yield, based on the recovery of **128** (11 mg): R_f 0.60 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 3524, 2955, 2912, 2877, 1718, 1459, 1374, 1189 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (major) 5.09 (m, 1H), 4.95 (m, 1H), 4.16 (m, 2H), 4.09 (m, 2H), 3.40 – 3.30 (br s, 1H), 2.78 (d, J_{AB} = 15.7 Hz, 1H), 2.34 (d, J_{AB} = 15.6 Hz, 1H), 2.08 (dd, J = 14.5, 6.4 Hz, 1H), 2.02 - 1.86 (m, 2H), 1.83 – 1.70 (m, 2H), 1.64 – 1.56 (m, 1H), 1.33 – 1.25 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H), 1.14 (dddd, J = 13.9, 9.2, 7.2, 5.8 Hz, 1H), 0.98 (d, J = 6.6 Hz, 3H), 0.97 (t, J = 7.8 Hz, 9H), 0.62 (q, J = 7.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (major) 173.2, 147.7, 110.4, 80.4, 65.7, 60.5, 53.8, 44.3, 38.7, 38.6, 31.3, 30.9, 20.5, 14.2, 6.8, 4.4; (minor) 173.6, 147.0, 110.7, 81.4, 65.3, 60.7, 53.9, 40.5, 39.0, 38.6, 34.5, 31.1, 21.4, 14.2, 6.8, 4.4; HRMS (EI) calcd for $C_{20}H_{38}O_4Si$ 370.2539; found 370.2537.

Allyl Bromide 136: To a stirred solution of **134** (44 mg, 0.17 mmol, 1 equiv) in Et_2O (1 mL) was added a 1 % (v/v) solution of PBr_3 in Et_2O (73 *m*L, 0.46 equiv) and the solution stirred for 15 min. at 0 °C. T.L.C. analysis of the reaction mixture indicated consumption of **134**, so the mixture was purified by passing through a plug of silica, eluting with Et_2O, to afford 24 mg of **136** as a clear oil in 44 % yield. The major isomer: R_f 0.52 (30% EtOAc / hexanes); IR (CH_2Cl_2 cast) 3522, 2952, 2868, 1732, 1717, 1540, 1457, 1372, 1209, 1190 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.21 (m, 1H), 5.08 (q, J = 1.3 Hz, 1H), 4.18 (m, 2H), 4.01 (d, J = 0.8 Hz, 2H), 2.75 (d, J_{AB} = 15.8 Hz, 1H), 2.59 (dd, J = 15.9, 6.1 Hz, 1H), 2.31 (d, J_{AB} = 15.8 Hz, 1H), 2.26 (ddd, J = 15.9, 6.9, 0.6 Hz, 1H), 2.01 (m, 1H), 1.93 (ddd, J = 15.7, 9.0, 6.6 Hz, 1H), 1.85 – 1.72 (m, 2H), 1.30 – 1.24 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H), 1.16 (dddd, J = 16.6, 9.5, 7.2, 5.4 Hz, 1H), 0.99 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (major) 173.2, 147.7, 116.8, 80.4, 60.7, 53.2, 44.0, 38.8, 38.7, 36.5, 32.3, 30.9, 20.7, 14.2; HRMS (EI) calcd for $C_{14}H_{23}O_3$ (M-Br) 239.16472; found 239.16443. The alcohol proton was not observed in the ^1H NMR spectrum.

Ether 137: In a 2 mL vial was added NaH (60 % in oil; 3 mg, 1.1 equiv) and this was rinsed with hexanes. The hexanes was decanted, then a solution of **136** in DME (0.6 mL) was added via cannula and the reaction mixture was stirred for an hour, at which time T.L.C. analysis indicated the consumption of **136**. The reaction was diluted with Et_2O (1 mL) and quenched by the addition of saturated aqueous NH_4Cl (1 mL). The layers were separated, and the aqueous layer was diluted with water (5 mL) and extracted twice with ether (10 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, then concentrated to give 15 mg of **137** in 95 % crude yield: R_f 0.59 (30 % EtOAc / hexanes); IR (CH_2Cl_2 cast) 2952, 2929, 2868, 1736, 1461, 1369, 1191 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.83 (m, 1H), 4.77 (m, 1H), 4.24 (d, J_{AB} = 13.4 Hz, 1H), 4.15 (q, J = 7.1 Hz, 1H), 3.96 (d, J_{AB} = 13.4 Hz, 1H), 2.99 (d, J_{AB} = 13.4 Hz, 1H), 2.50 (m, 1H), 2.45 (d, J_{AB} = 13.4 Hz, 1H), 2.24 (d, J = 14.5 Hz, 1H), 2.04 - 1.92 (m, 3H), 1.82 (d, J = 14.0, 8.4 Hz, 1H), 1.37 (ddd, J = 10.1, 5.6, 3.0Hz, 1H), 1.26 (t, J = 7.1 Hz, 3H), 1.15 (m, 1H), 0.96 (d, J = 6.4 Hz, 3H; ^{13}C NMR (125 MHz, $CDCl_3$) δ (major) 170.9, 141.4, 110.1, 82.1, 66.1, 60.3, 51.2, 39.7, 37.1, 35.1, 31.0, 29.7, 18.8, 14.2; HRMS (EI) calcd for $C_{14}H_{22}O_3$ 328.1569; found 238.1567.

4.6. References

1. Schmitz, F. J.; Hollenbeak, K. H.; Vanderah, D. J., Marine Natural-Products - Dactylol, a New Sesquiterpene Alcohol from a Sea Hare. *Tetrahedron* **1978**, 34, (18), 2719-2722.

2. Fenical, W.; Schulte, G. R.; Finer, J.; Clardy, J., Poitediol, a New Nonisoprenoid Sesquiterpene Diol from Marine Alga Laurencia-Poitei. *J. Org. Chem.* **1978**, 43, (18), 3628-3630.

3. Hayasaka, K.; Ohtsuka, T.; Shirahama, H.; Matsumoto, T., Chemical Conversion of Humulene to Dactylol - Biomimetic, Apparent 1,2-Shift of a Methyl-Group. *Tetrahedron Lett.* **1985**, 26, (7), 873-876.

4. Paquette, L. A.; Ham, W. H., Total Synthesis of the Marine Sesquiterpenes Dactylol and Africanol - Denovo Construction of a Cyclooctanoid Natural Product from Cycloheptane Precursors. *J. Am. Chem. Soc.* **1987**, 109, (10), 3025-3036.

5. Paquette, L. A.; Ham, W. H.; Dime, D. S., A Formal Total Synthesis of Dactylol. *Tetrahedron Lett.* **1985**, 26, (41), 4983-4986.

6. Shirahama, H.; Hayano, K.; Kanemoto, Y.; Misumi, S.; Ohtsuka, T.; Hashiba, N.; Furusaki, A.; Murata, S.; Noyori, R.; Matsumoto, T., Conformationally Selective Trans-Annular Cyclizations of Humulene 9,10-Epoxide - Synthesis of the 2 Skeletally Different Cyclohumulanoids - Dl-Bicyclohumulenone and Dl-Africanol. *Tetrahedron Lett.* **1980**, 21, (50), 4835-4838.

7. Adams, R.; Shriner, R. L., Platinum Oxide as a Catalyst in the Reduction of Organic Compounds Iii Preparation and Properties of the Oxide of Platinum Obtained by the Fusion of Ceiloroplatinic Acid with Sodium Nitrate. *J. Am. Chem. Soc.* **1923**, 45, 2171-2179.

8. Carothers, W. H.; Adams, R., Platinum Oxide as a Catalyst in the Reduction of Organic Compounds II Reduction of Aldehydes Activation of the Catalyst by the Salts of Certain Metals. *J. Am. Chem. Soc.* **1923**, 45, 1071-1086.

9. Voorhees, V.; Adams, R., The Use of the Oxides of Platinum for the Catalytic Reduction of Organic Compounds I. *J. Am. Chem. Soc.* **1922**, 44, 1397-1405.

10. Hiyama, T.; Mishima, T.; Kitatani, K.; Nozaki, H., Preparation of Beta-Methylated Alpha,Beta-Unsaturated Ketones Via Dichlorocarbene Adducts of Enol Ethers - Synthesis of Dl-Muscone from Cyclotetradecanone. *Tetrahedron Lett.* **1974**, (37), 3297-3300.

11. Ito, Y.; Fujii, S.; Saegusa, T., Reaction of 1-Silyloxybicyclo[N.1.0]Alkanes with Feiiicl-3 - Facile Synthesis of 2-Cycloalkenones Via Ring Enlargement of Cyclic Ketones. *J. Org. Chem.* **1976**, 41, (11), 2073-2074.

12. Blanco, L.; Amice, P.; Conia, J. M., Reaction of Chloromethylcarbene with Trimethylsilyl Enol Ethers - Conversion of Cycloalkanones into Higher Alpha-Methylcycloalkenones. *Synthesis-Stuttgart* **1981**, (4), 289-291.

13. Sawada, S.; Inouye, Y., Partial Asymmetric Synthesis in Simmons-Smith Reaction .3. A Modification of Reaction. *Bull. Chem. Soc. Jpn.* **1969**, 42, (9), 2669.

14. Luche, J. L., Lanthanides in Organic-Chemistry .1. Selective 1,2 Reductions of Conjugated Ketones. *J. Am. Chem. Soc.* **1978**, 100, (7), 2226-2227.

15. Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehmann, W. J., Remote Double-Bond Migration Via Rhodium Catalysis - Novel Enone Transposition. *J. Am. Chem. Soc.* **1976**, 98, (22), 7102-7104.

16. Gadwood, R. C., Stereoelectronic Effects in Cyclo-Octanes - Synthesis of (+/-)-Dactylol and (+/-)-Isodactylol. *J. Chem. Soc., Chem. Commun.* **1985**, (3), 123-124.

17. Birch, A. J., Reduction by Dissolving Metals .2. *Journal of the Chemical Society* **1945**, (NOV-), 809-813.

18. Birch, A. J.; The Reduction of Organic Compounds by Metal-Ammonia Solutions. *Quarterly Reviews* **1950**, 4, (1), 69-93.

19. Gadwood, R. C.; Lett, R. M., Preparation and Rearrangement of 1,2-Dialkenylcyclobutanols - a Useful Method for Synthesis of Substituted Cyclooctenones. *J. Org. Chem.* **1982**, 47, (12), 2268-2275.

20. Gadwood, R. C.; Lett, R. M.; Wissinger, J. E., Total Synthesis of (+/-)-Poitediol and (+/-)-Dactylol. *J. Am. Chem. Soc.* **1986**, 108, (20), 6343-6350.

21. Jager, V.; Gunther, H. J., Synthesis of Gamma-Methylene Butyrolactones (4-Penten-4-Olides). *Tetrahedron Lett.* **1977**, (29), 2543-2546.

22. Johnson, W. S.; Werthema.L; Bartlett, W. R.; Brocksom, T. J.; Li, T. T.; Faulkner, D. J.; Petersen, M. R., A Simple Stereoselective Version of Claisen Rearrangement Leading to Trans-Trisubstituted Olefinic Bonds . Synthesis of Squalene. *J. Am. Chem. Soc.* **1970**, 92, (3), 741.

23. Feldman, K. S.; Come, J. H.; Fegley, G. J.; Smith, B. D.; Parvez, M., Synthesis of the Barbaralone Nucleus Via Photocyclization of an Alkynyl Tropone. *Tetrahedron Lett.* **1987**, 28, (6), 607-610.

24. Feldman, K. S.; Come, J. H.; Freyer, A. J.; Kosmider, B. J.; Smith, C. M., Synthesis of 8-Membered Carbocycles Via Intramolecular [6-Pi+2-Pi] Photocycloaddition of Alkenyltropones. *J. Am. Chem. Soc.* **1986**, 108, (6), 1327-1328.

25. Feldman, K. S.; Come, J. H.; Kosmider, B. J.; Smith, P. M.; Rotella, D. P.; Wu, M. J., Mechanistic and Preparative Studies of the Intramolecular Photocyclization of Methylated 2-(4-Pentenyl)Tropones. *J. Org. Chem.* **1989**, 54, (3), 592-601.

26. Feldman, K. S.; Wu, M. J.; Rotella, D. P., Application of an Intramolecular Tropone Alkene Photocyclization to the Total Synthesis of (+/-)-Dactylol. *J. Am. Chem. Soc.* **1989**, 111, (16), 6457-6458.

27. Feldman, K. S.; Wu, M. J.; Rotella, D. P., Total Synthesis of (+/-)-Dactylol and Related Studies. *J. Am. Chem. Soc.* **1990**, 112, (23), 8490-8496.

28. Funk, R. L.; Bolton, G. L., Intramolecular [6+4] and [4+2] Tropone Olefin Cycloaddition Reactions - Facile Synthesis of the Ingenane Ring-System. *J. Am. Chem. Soc.* **1986**, 108, (15), 4655-4657.

29. Corey, E. J.; Kang, M.; Desai, M. C.; Ghosh, A. K.; Houpis, J. N., Total Synthesis of (+/-)-Ginkgolide-B. *J. Am. Chem. Soc.* **1988**, 110, (2), 649-651.

30. Pete, J. P.; Portella, C.; Monneret, C.; Florent, J. C.; Qui, K. H., General and Convenient Photochemical Method for Preparation of Deoxysugars. *Synthesis-Stuttgart* **1977**, (11), 774-776.

31. Molander, G. A.; Eastwood, P. R., Total Synthesis of (+)-Dactylol Via a Novel [3+5]-Annulation Approach. *J. Org. Chem.* **1995**, 60, (14), 4559-4565.

32. Molander, G. A.; Andrews, S. W., Bis(Trimethylsilyl) Enol Ethers as 1,3-Dianion Equivalents - Regiocontrolled [3+4] and [3+5] Annulation Reactions. *Tetrahedron Lett.* **1989**, 30, (18), 2351-2354.

33. Molander, G. A.; Shubert, D. C., Stereocontrolled [M+N] Annulation Reactions .3. A Convenient Approach to 7-Membered and 8-Membered Carbocycles by a Novel Annulation Process. *J. Am. Chem. Soc.* **1987**, 109, (22), 6877-6878.

34. Molander, G. A.; Cameron, K. O., A Novel Concept for Regiochemical and Stereochemical Control in Lewis Acid Promoted [3+4] Annulation Reactions. *J. Org. Chem.* **1991**, 56, (8), 2617-2619.

35. Molander, G. A.; Cameron, K. O., Neighboring Group Participation in Lewis Acid-Promoted [3+4] and [3+5] Annulations - the Stereocontrolled Synthesis of Tricyclic Ethers. *J. Org. Chem.* **1993**, 58, (22), 5931-5943.

36. Molander, G. A.; Cameron, K. O., Neighboring Group Participation in Lewis Acid-Promoted [3+4] and [3+5] Annulations - the Synthesis of Oxabicyclo[3.N.1]Alkan-3-Ones. *J. Am. Chem. Soc.* **1993**, 115, (3), 830-846.

37. Molander, G. A.; Siedem, C. S., Regioselectivity in [3+4]-Annulation and [3+5]-Annulation Reactions of Bis(Trimethylsilyl) Enol Ethers with Acylsilane Dicarbonyl Dielectrophiles. *J. Org. Chem.* **1995**, 60, (1), 130-138.

38. Marx, J. N.; Norman, L. R., Synthesis of (-)-Acorone and Related Spirocyclic Sesquiterpenes. *J. Org. Chem.* **1975**, 40, (11), 1602-1606.

39. Krapcho, A. P., Synthetic Applications of Dealkoxycarbonylations of Malonate Esters, Beta-Keto-Esters, Alpha-Cyano Esters and Related-Compounds in Dipolar Aprotic Media .1. *Synthesis-Stuttgart* **1982**, (10), 805-823.

40. Tebbe, F. N.; Parshall, G. W.; Reddy, G. S., Olefin Homologation with Titanium Methylene-Compounds. *J. Am. Chem. Soc.* **1978**, 100, (11), 3611-3613.

41. Rigby, J. H.; Wilson, J. A. Z., A General-Approach to the Synthesis of C-8-Oxygenated Guaianolides. *J. Org. Chem.* **1987**, 52, (1), 34-44.

42. Grubbs, R. H.; Miller, S. J.; Fu, G. C., Ring-Closing Metathesis and Related Processes in Organic-Synthesis. *Acc. Chem. Res.* **1995**, 28, (11), 446-452.

43. Furstner, A.; Langemann, K., A Concise Total Synthesis of Dactylol Via Ring Closing Metathesis. *J. Org. Chem.* **1996**, 61, (25), 8746-8749.

44. Suzuki, M.; Kawagishi, T.; Suzuki, T.; Noyori, R., A Facile Synthesis of (-)-Prostaglandin E1 Via a 3-Component Coupling Process. *Tetrahedron Lett.* **1982**, 23, (39), 4057-4060.

45. Molander, G. A., Application of Lanthanide Reagents in Organic-Synthesis. *Chem. Rev.* **1992**, 92, (1), 29-68.

46. Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; Dimare, M.; Oregan, M., Synthesis of Molybdenum Imido Alkylidene Complexes and Some Reactions Involving Acyclic Olefins. *J. Am. Chem. Soc.* **1990**, 112, (10), 3875-3886.

47. Harmata, M.; Rashatasakhon, P., Intramolecular 4+3 Cycloadditions. Aspects of Stereocontrol in the Synthesis of Cyclooctanoids. A Synthesis of (+)-Dactylol. *Org. Lett.* **2000**, 2, (18), 2913-2915.

48. Wang, Y.; Arif, A. M.; West, F. G., A Novel Cycloisomerization of Tetraenones: 4+3 Trapping of the Nazarov Oxyallyl Intermediate. *J. Am. Chem. Soc.* **1999**, 121, (4), 876-877.

49. Harmata, M.; Elomari, S.; Barnes, C. L., Intramolecular 4+3 Cycloadditions. Cycloaddition Reactions of Cyclic Alkoxyallylic and Oxyallylic Cations. *J. Am. Chem. Soc.* **1996**, 118, (12), 2860-2871.

50. Huckin, S. N.; Weiler, L., Alkylation of Dianions of Beta-Keto-Esters. *J. Am. Chem. Soc.* **1974**, 96, (4), 1082-1087.

51. Wender, P. A.; Holt, D. A., Macroexpansion Methodology .3. 8-Step Synthesis of (-)-(3z)-Cembrene-A. *J. Am. Chem. Soc.* **1985**, 107, (25), 7771-7772.

52. Danishefsky, S.; Tsuzuki, K., Control of Remote Relative Chiralities - a Stereospecific Total Synthesis of Dl-Widdrol. *J. Am. Chem. Soc.* **1980**, 102, (22), 6891-6893.

53. Denney, D. B.; Sherman, N., Degradation of Acids to Alcohols by Carboxy-Inversion Reaction. *J. Org. Chem.* **1965**, 30, (11), 3760.

54. Kienzle, F.; Holland, G. W.; Jernow, J. L.; Kwoh, S.; Rosen, P., Versatile Prostaglandin Synthesis Use of a Carboxy-Inversion Reaction. *J. Org. Chem.* **1973**, 38, (19), 3440-3442.

55. Marmsäter, F. P. Generation and Rearrangements of Oxonium Ylides in Synthesis. The University of Utah, Utah, 2003.

56. Krapcho, A. P., Synthetic Applications of Dealkoxycarbonylations of Malonate Esters, Beta-Keto-Esters, Alpha-Cyano Esters and Related-Compounds in Dipolar Aprotic Media .2. *Synthesis-Stuttgart* **1982**, (11), 893-914.

57. Picotin, G.; Miginiac, P., Activation of Zinc by Trimethylchlorosilane - an Improved Procedure for the Preparation of Beta-Hydroxy Esters from Ethyl Bromoacetate and Aldehydes or Ketones (Reformatsky Reaction). *J. Org. Chem.* **1987**, 52, (21), 4796-4798.

58. Cohen, T.; Bhupathy, M., Organoalkali Compounds by Radical-Anion Induced Reductive Metalation of Phenyl Thioethers. *Acc. Chem. Res.* **1989**, 22, (4), 152-161.

59. Rychnovsky, S. D.; Buckmelter, A. J.; Dahanukar, V. H.; Skalitzky, D. J., Synthesis, Equilibration, and Coupling of 4-Lithio-1,3-Dioxanes: Synthons for Syn- and Anti-1,3-Diols. *J. Org. Chem.* **1999**, 64, (18), 6849-6860.

60. Dauben, W. G.; Michno, D. M., Direct Oxidation of Tertiary Allylic Alcohols - Simple and Effective Method for Alkylative Carbonyl Transposition. *J. Org. Chem.* **1977**, 42, (4), 682-685.

61. Schmitt, A.; Reissig, H. U., On the Stereoselectivity of Gamma-Lactol Substitutions with Allyl- and Propargylsilanes - Synthesis of Disubstituted Tetrahydrofuran Derivatives. *Eur. J. Org. Chem.* **2000**, (23), 3893-3901.

62. Schmitt, A.; Reissig, H. U., On the Stereoselectivity of Gamma-Lactol Substitutions with Allyl- and Propargylsilanes - Synthesis of Disubstituted Tetrahydrofuran Derivatives. *Eur. J. Org. Chem.* **2000**, (23), 3893-3901.

63. Trost, B. M.; Grese, T. A.; Chan, D. M. T., Intramolecular Palladium-Catalyzed Trimethylenemethane Cycloadditions - Initial Studies. *J. Am. Chem. Soc.* **1991**, 113, (19), 7350-7362.

64. Tzeng, D.; Weber, W. P., Reaction of Allylic and Benzylic Methyl Ethers with Sodium and Trimethylchlorosilane - Evidence for the Intermediacy of Allylic Radicals and Anions. *J. Org. Chem.* **1981**, 46, (2), 265-267.

65. Smith, A. B.; Levenberg, P. A.; Jerris, P. J.; Scarborough, R. M.; Wovkulich, P. M., Synthesis and Reactions of Simple 3(2h)-Furanones. *J. Am. Chem. Soc.* **1981**, 103, (6), 1501-1513.

66. Chandrasekhar, S.; Narsihmulu, C.; Saritha, B.; Sultana, S. S., Poly(Ethyleneglycol) (Peg): A Rapid and Recyclable Reaction Medium for the Dabco-Catalyzed Baylis-Hillman Reaction. *Tetrahedron Lett.* **2004**, 45, (30), 5865-5867.

67. Villieras, J.; Rambaud, M., Ethyl Alpha-(Hydroxymethyl)Acrylate. *Org. Synth.* **1988**, 66, 220-224.

68. Taber, D. F.; Amedio, J. C.; Patel, Y. K., Preparation of Beta-Keto-Esters by 4-Dmap-Catalyzed Ester Exchange. *J. Org. Chem.* **1985**, 50, (19), 3618-3619.

69. Witzeman, J. S., The Transacetoacetylation Reaction - Mechanistic Implications. *Tetrahedron Lett.* **1990**, 31, (10), 1401-1404.

70. Otera, J., Transesterification. *Chem. Rev.* **1993**, 93, (4), 1449-1470.

71. Otera, J.; Danoh, N.; Nozaki, H., Novel Template Effects of Distannoxane Catalysts in Highly Efficient Transesterification and Esterification. *J. Org. Chem.* **1991**, 56, (18), 5307-5311.

72. Stanton, M. G.; Gagne, M. R., A Mild Protocol for the Conversion of Simple Esters to Tert-Butyl Esters. *J. Org. Chem.* **1997**, 62, (23), 8240-8242.

73. Stanton, M. G.; Gagne, M. R., The Remarkable Catalytic Activity of Alkali-Metal Alkoxide Clusters in the Ester Interchange Reaction. *J. Am. Chem. Soc.* **1997**, 119, (21), 5075-5076.

74. Tamura, O.; Shiro, T.; Ogasawara, M.; Toyao, A.; Ishibashi, H., Stereoselective Syntheses of 4-Hydroxy 4-Substituted Glutamic Acids. *J. Org. Chem.* **2005**, 70, (12), 4569-4577.

75. Burger, E. C.; Tunge, J. A., Ruthenium-Catalyzed Decarboxylative Allylation of Nonstabilized Ketone Enolates. *Org. Lett.* **2004**, 6, (15), 2603-2605.

76. Burger, E. C.; Tunge, J. A., Ruthenium-Catalyzed Stereospecific Decarboxylative Allylation of Non-Stabilized Ketone Enolates. *Chem. Commun.* **2005**, (22), 2835-2837.

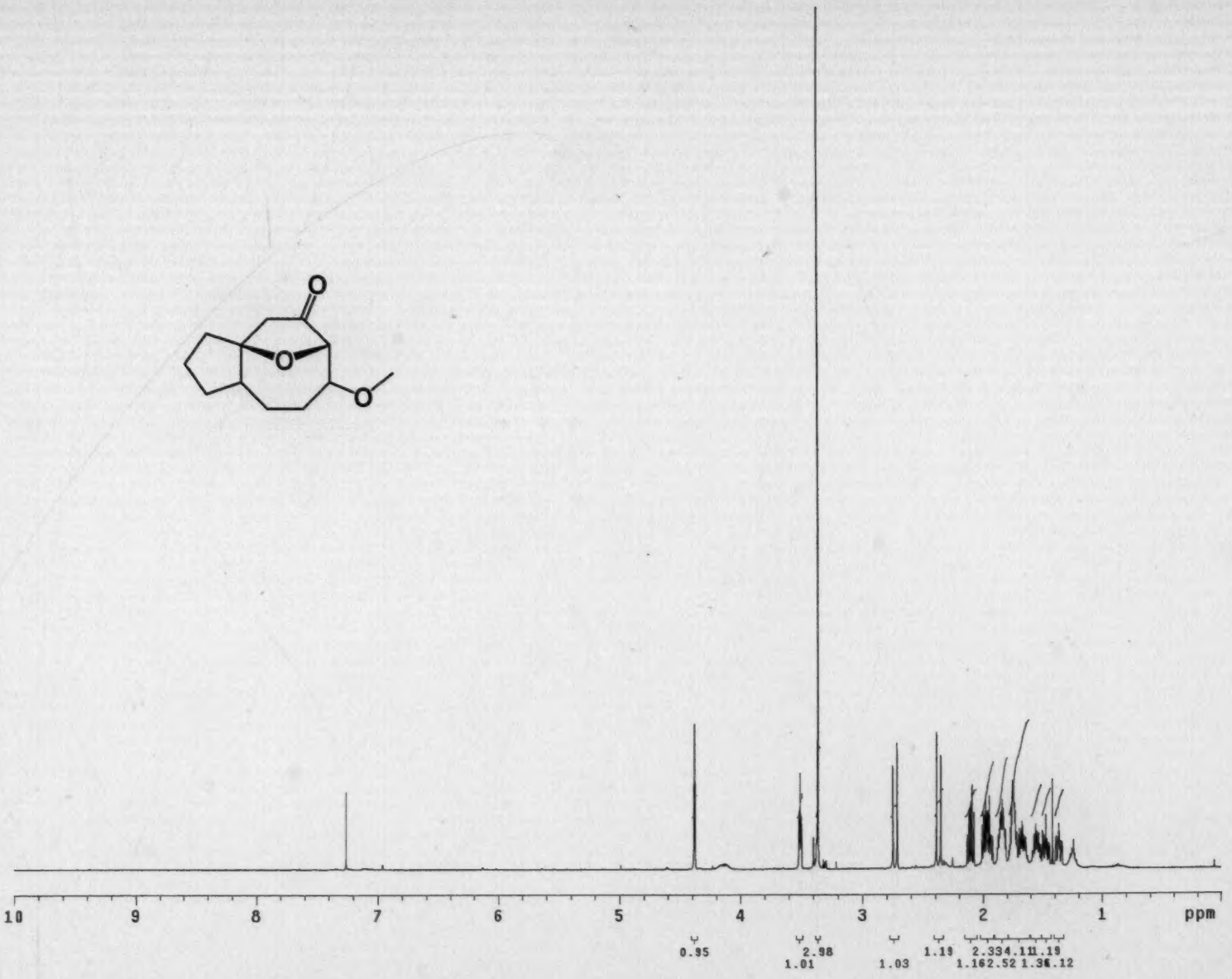
77. Tunge, J. A.; Burger, E. C., Transition Metal Catalyzed Decarboxylative Additions of Enolates. *Eur. J. Org. Chem.* **2005**, (9), 1715-1726.

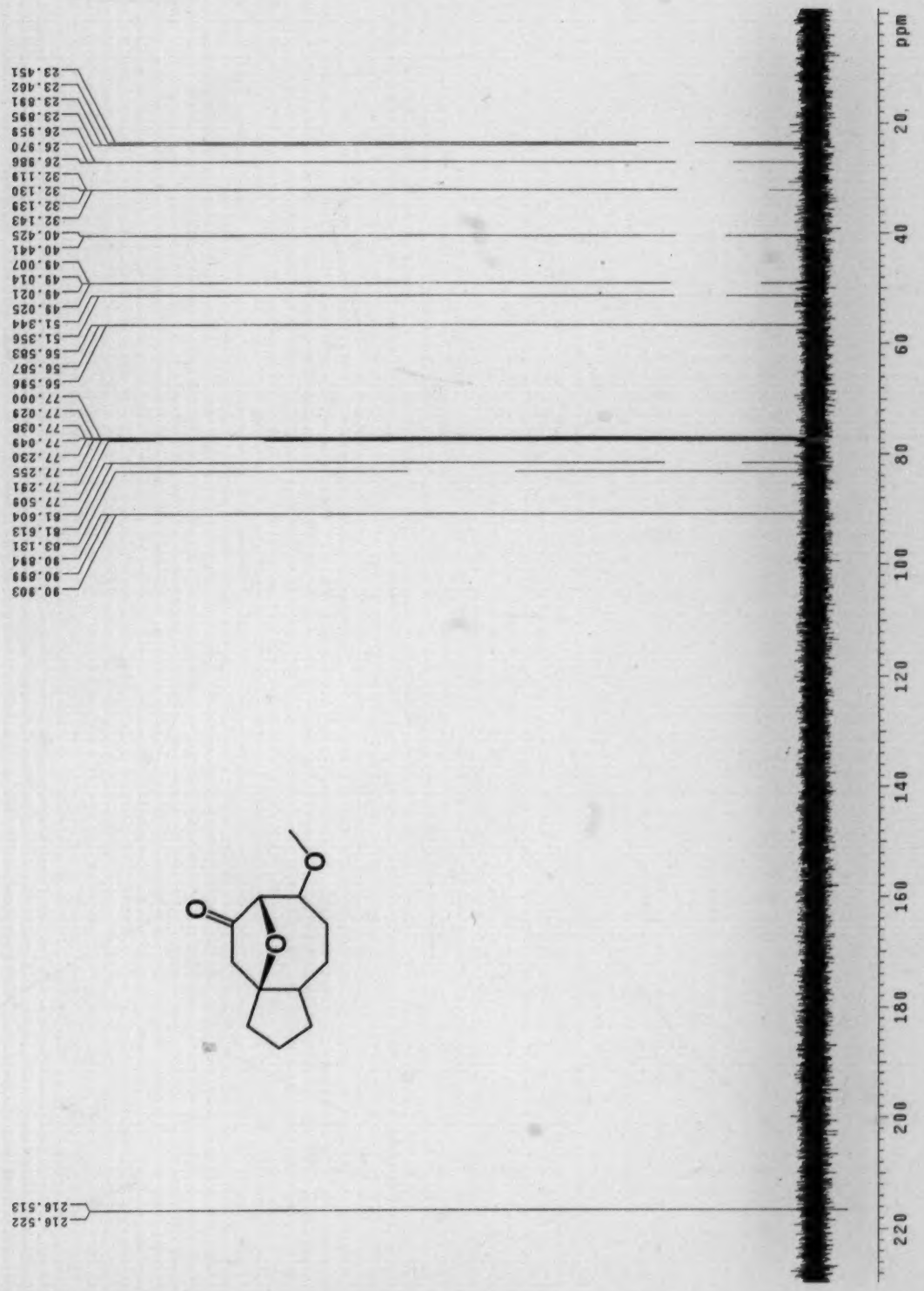
78. Tsuda, T.; Chujo, Y.; Nishi, S.-I.; Tawara, K.; Saegusa, T., Facile Generation of a Reactive Palladium (II) Enolate Intermediate by the Decarboxylation of Palladium (II) β-ketocarboxylate and its Utilization in Allylic Acylation. *J. Am. Chem. Soc.* **1980**, *102*, 6381-6384.

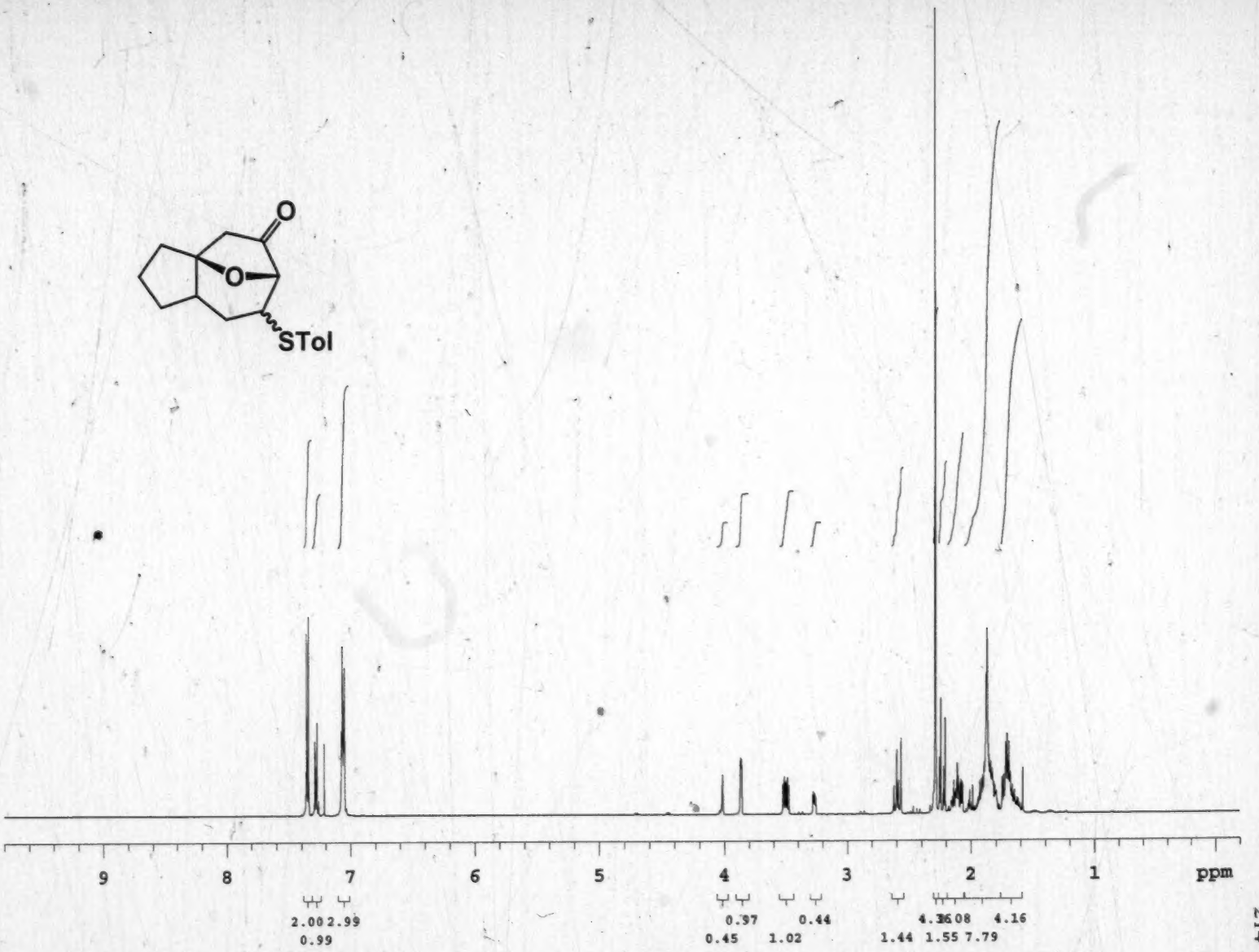
79. Tsuji, J., Catalytic Reactions via π-Allylpalladium Complexes. *Pure Appl. Chem.* **1982**, *54*, 197-206.

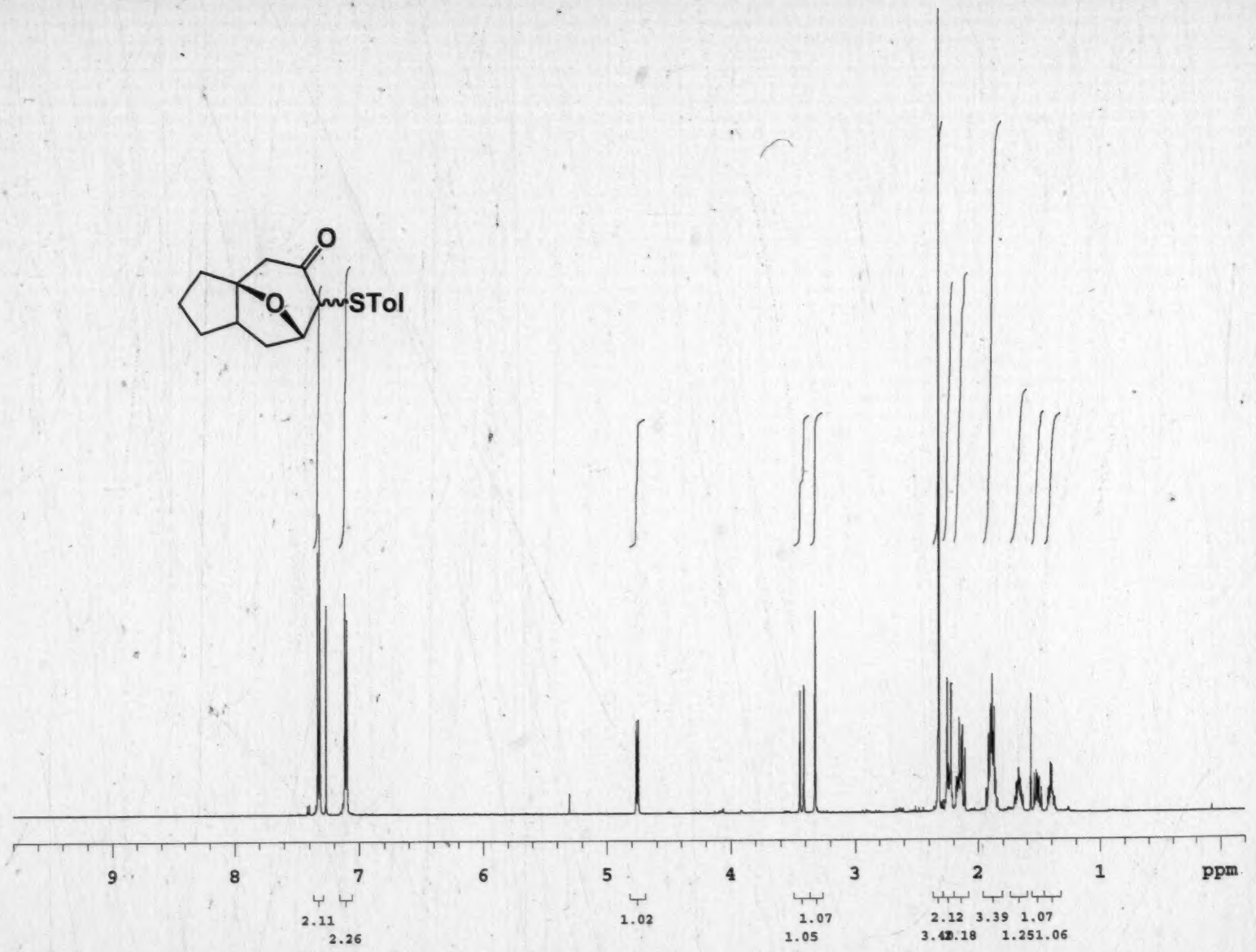
80. Tsuji, J.; Yamada, T.; Minami, I.; Yuhara, M.; Nisar, M.; Shimizu, I., Palladium-Catalyzed Decarboxylation-Allylation of Allylic Esters of α-Substituted-β-keto Carboxylic, Malonic, Cyanoacetic, and Nitroacetic Acids. *J. Org. Chem.* **1987**, *52*, 2988-2995.

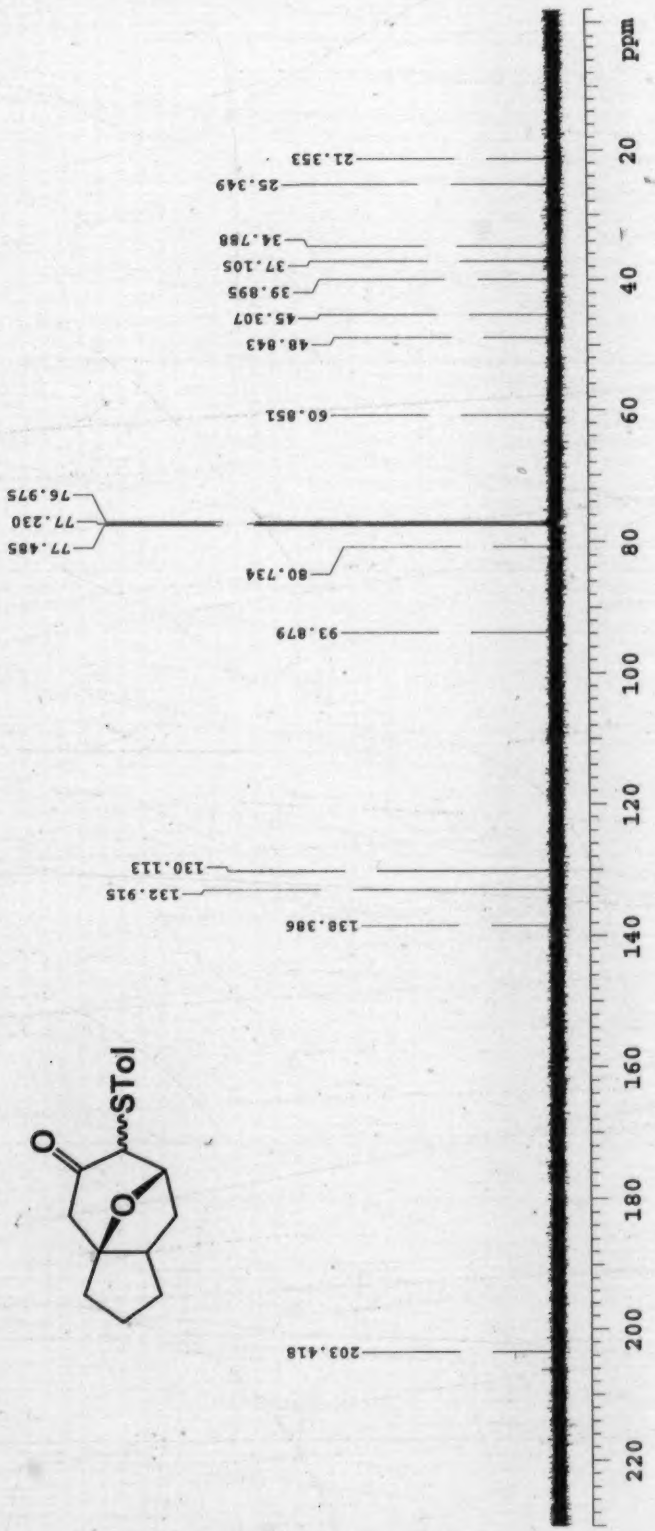
Appendix Chapter 2

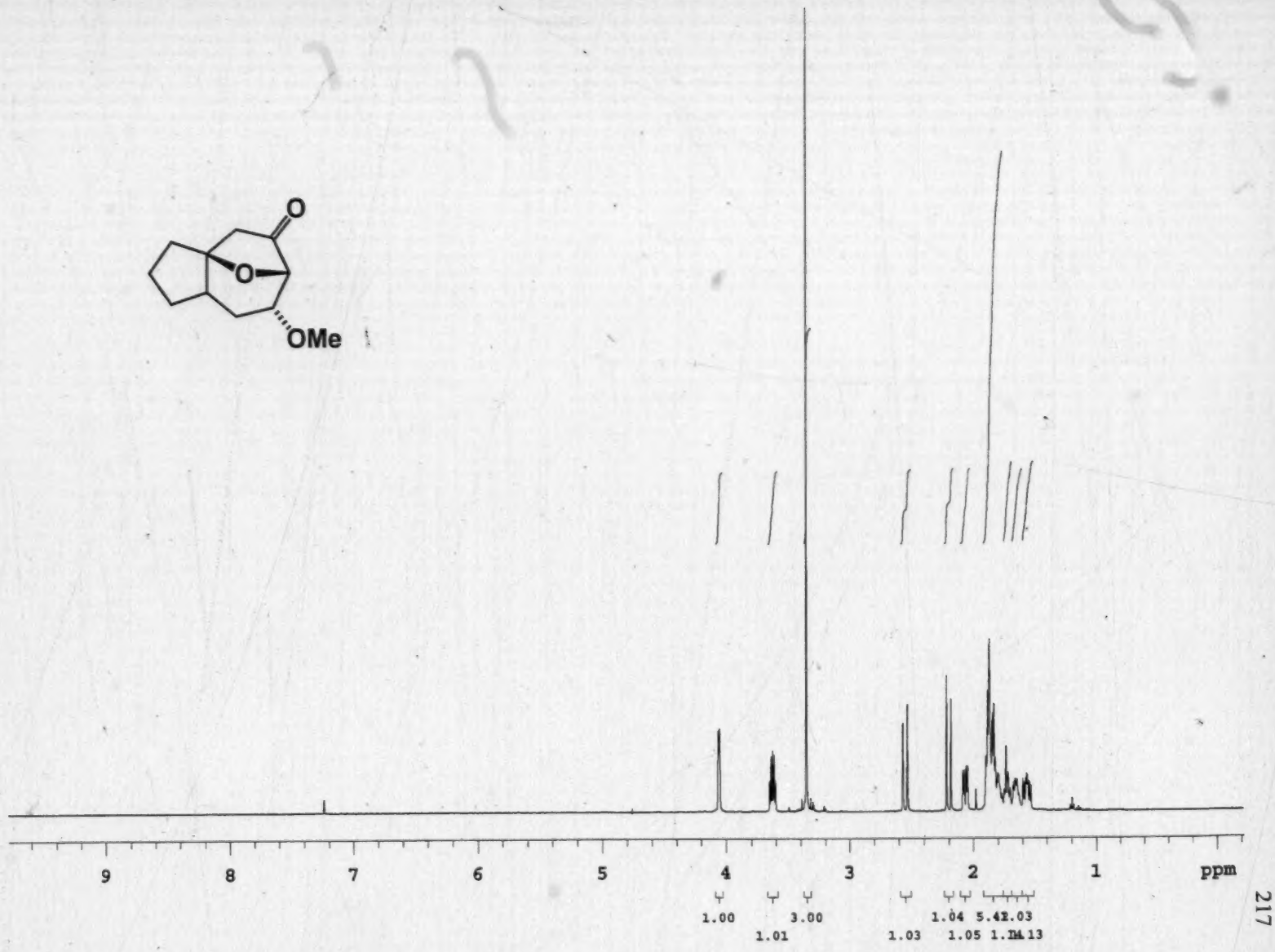

O
O
O
10
9
8
7
6
5
4
3
2
1
ppm
0.95
2.98
1.01
1.03
1.19
2.33
4.11
1.19
1.16
2.52
1.36
4.12

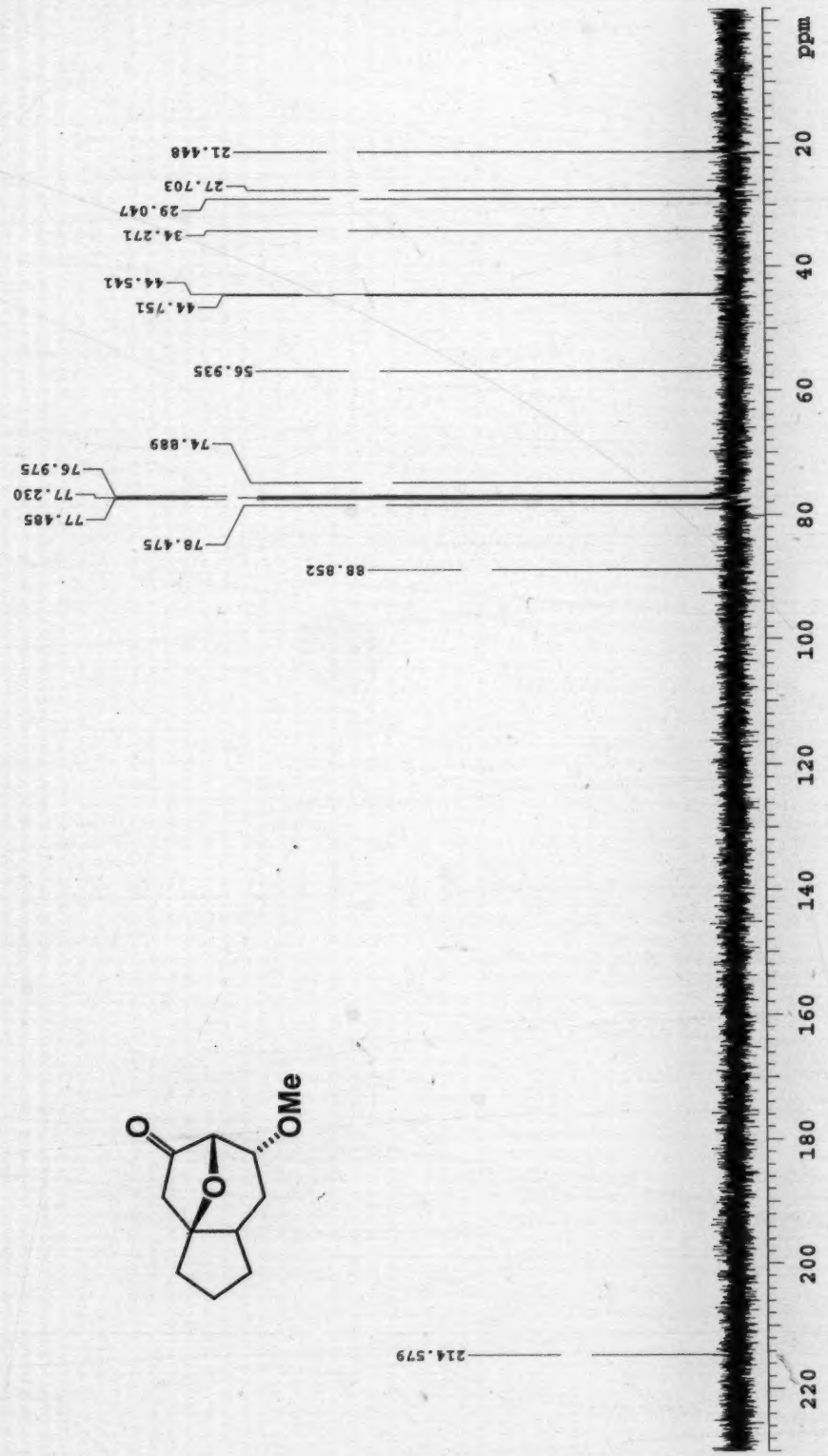

23.451
23.462
23.691
23.895
26.959
26.970
26.986
32.119
32.130
32.139
32.143
40.425
40.441
49.007
49.014
49.021
49.025
51.344
51.356
56.583
56.587
56.596
77.000
77.029
77.038
77.049
77.230
77.255
77.291
77.509
81.604
81.613
83.131
90.894
90.899
90.903
216.513
216.522
ppm
20
40
60
80
100
120
140
160
180
200
220

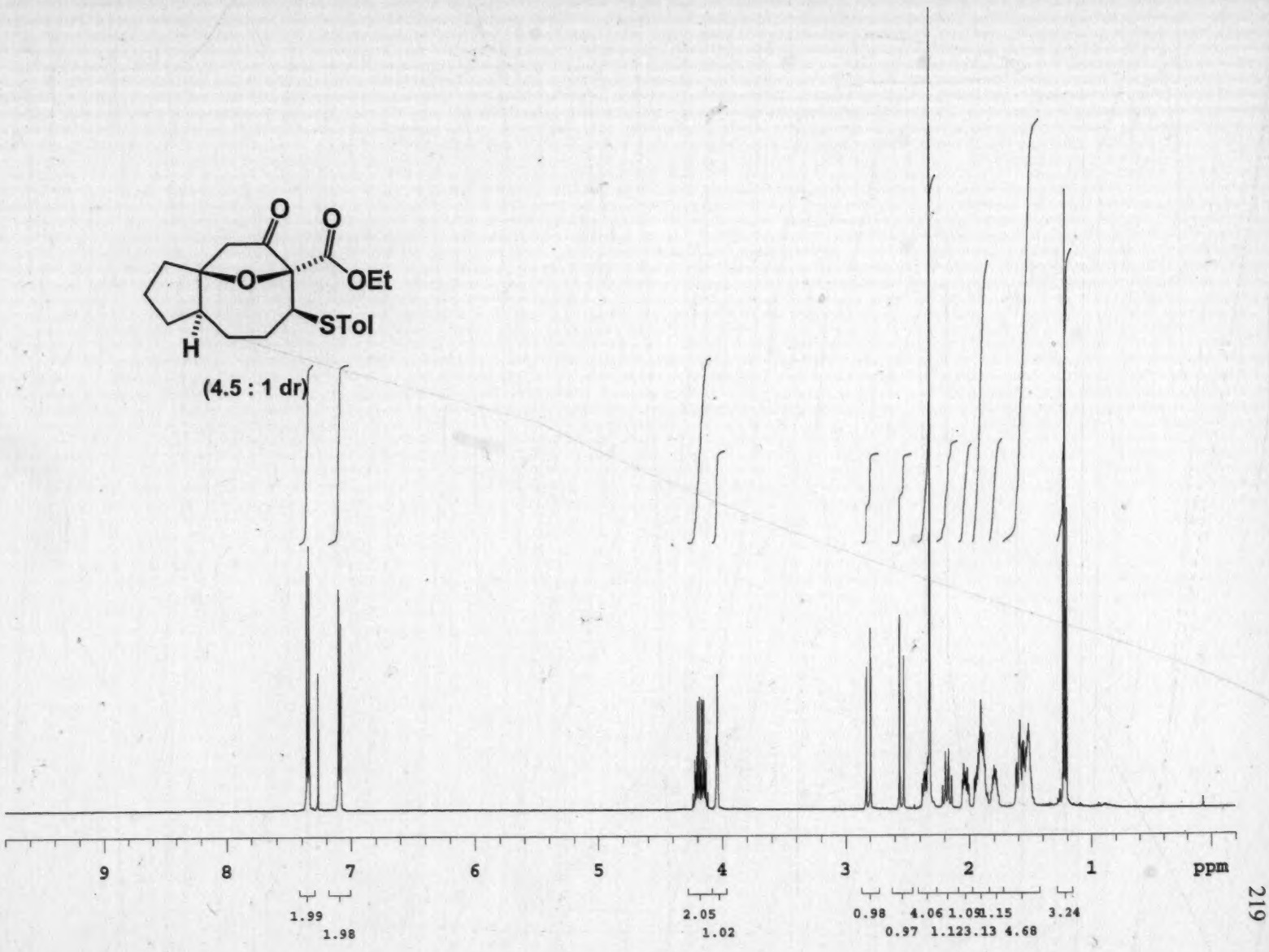

O
O
STol
9
8
7
6
5
4
3
2
1
ppm
2.00 2.99
0.99
0.97
0.44
0.45
1.02
1.44
1.55
7.79
4.16

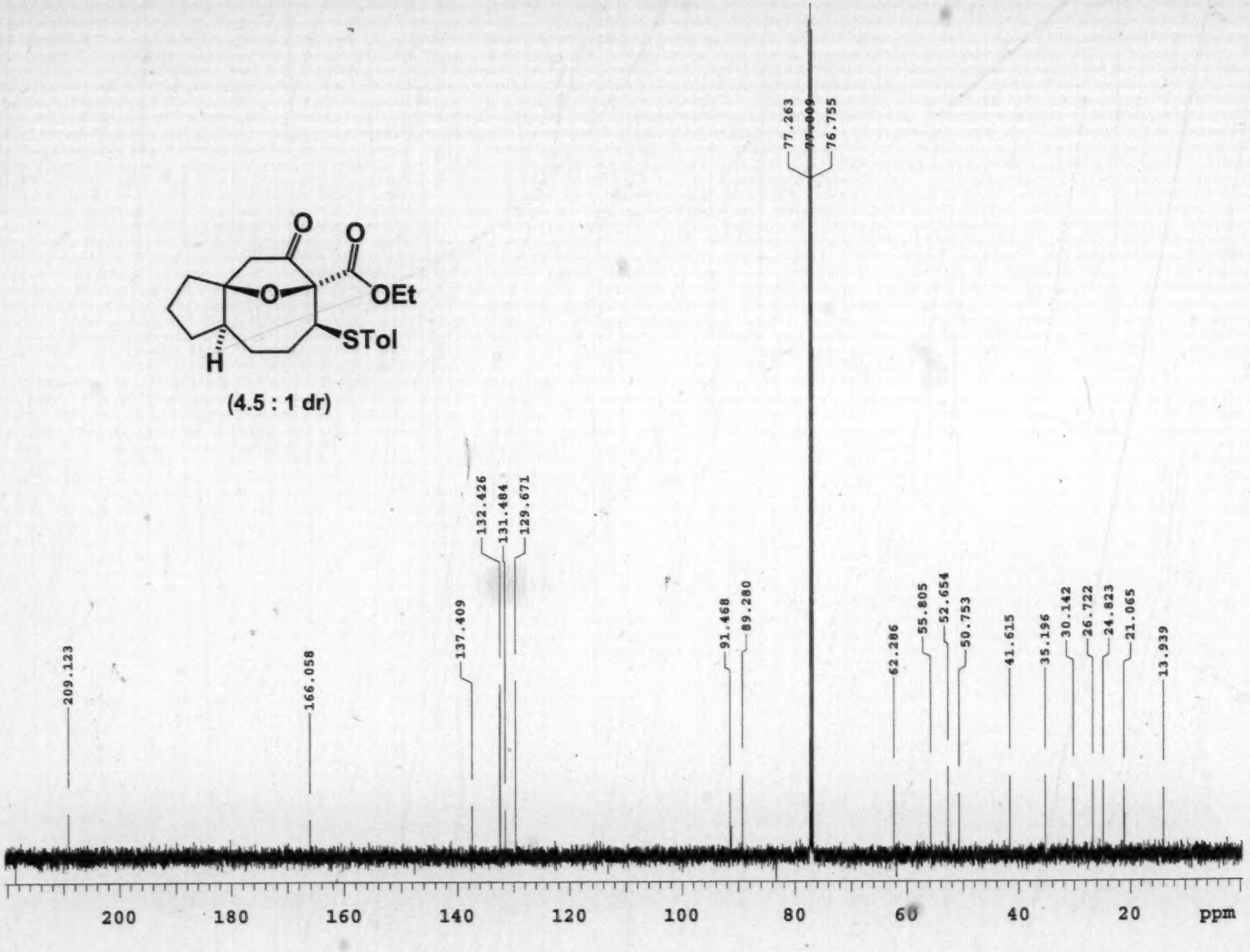

O
O
STol
9
8
7
6
5
4
3
2
1
ppm
2.11
2.26
1.02
1.07
1.05
2.12
3.39
1.07
1.25
1.06

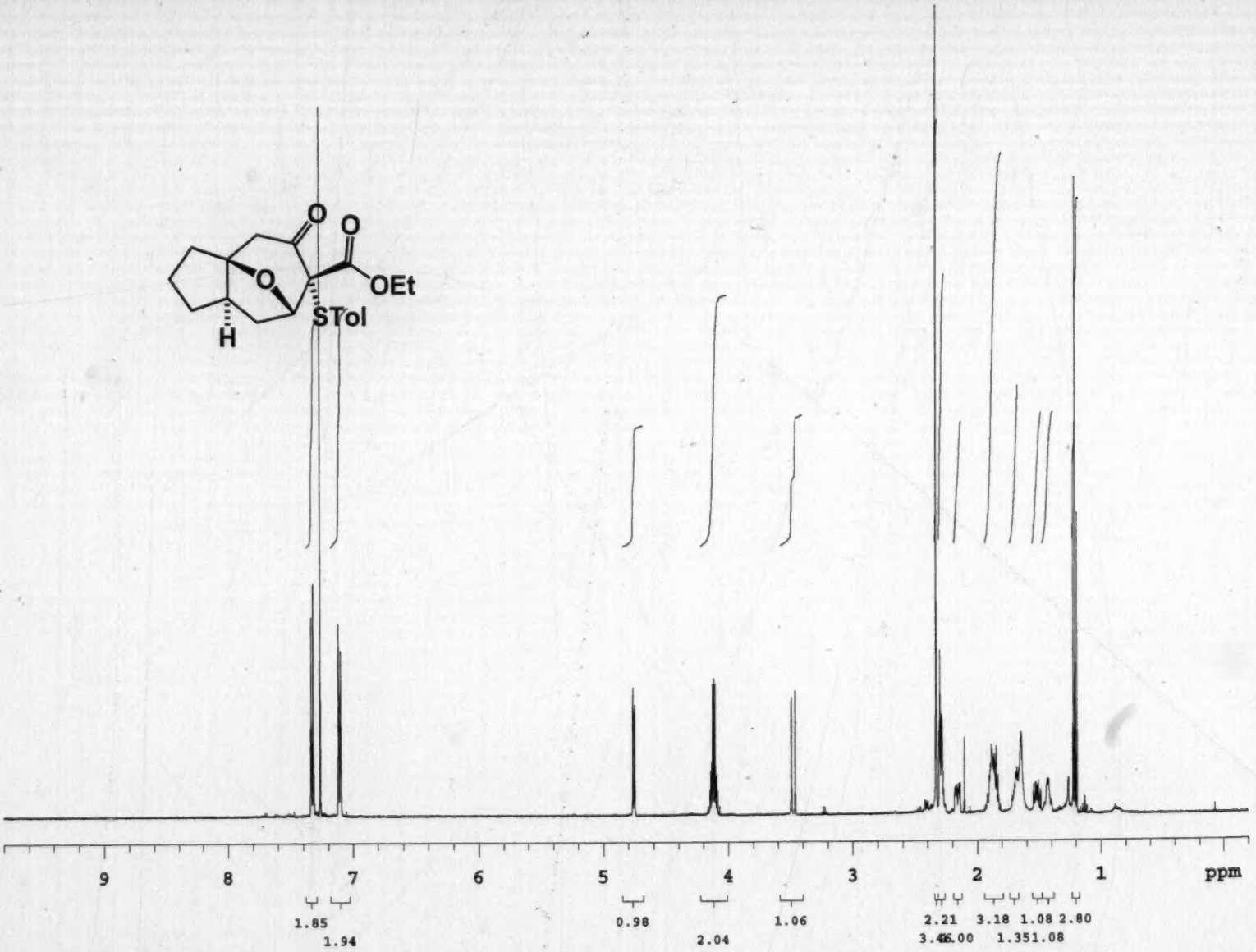

ppm
20
40
60
80
100
120
140
160
180
200
220
21.353
25.349
34.788
37.105
39.895
45.307
48.843
60.851
76.975
77.230
77.485
80.734
93.879
130.113
132.915
138.386
203.418
STol
O
O


O
O
OMe
9
8
7
6
5
4
3
2
1
ppm
1.00
1.01
3.00
1.03
1.04
1.05
5.41
1.13
2.03

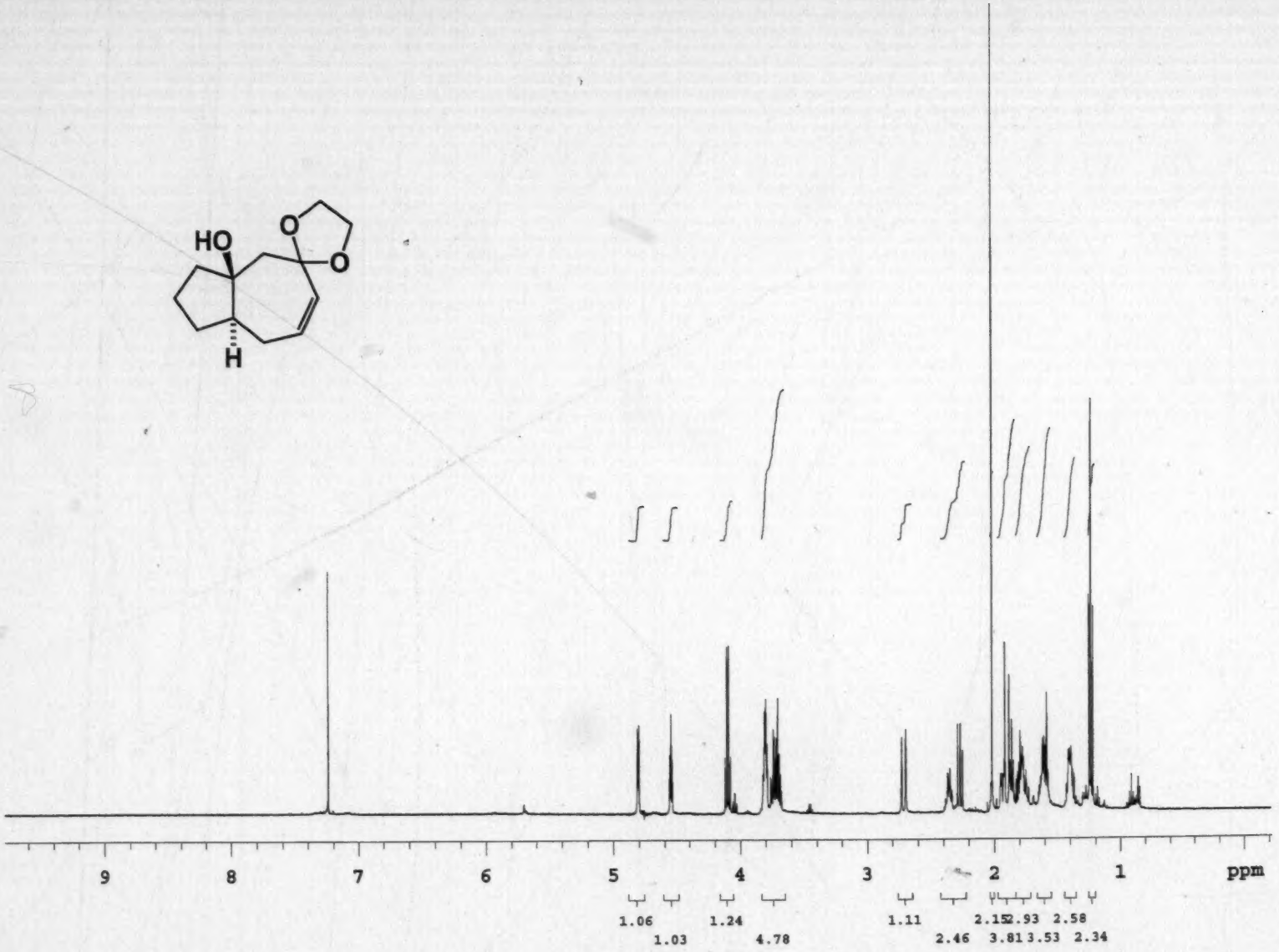

214.579
88.852
78.475
77.485
77.230
76.975
74.889
56.935
44.751
44.541
34.271
29.047
27.703
21.448
ppm
220
200
180
160
140
120
100
80
60
40
20
OMe
O
O

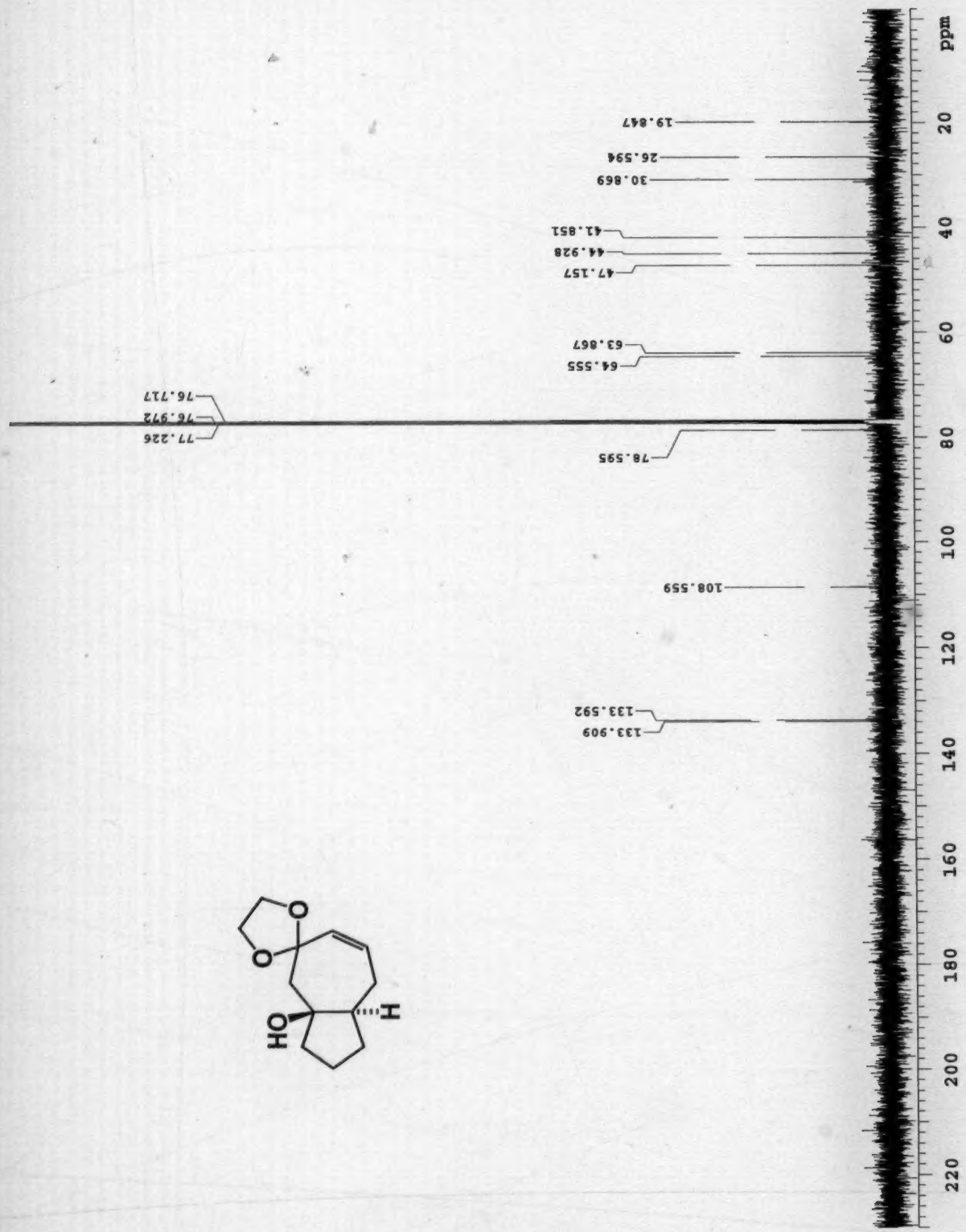

O
O
O
OEt
STol
H
(4.5 : 1 dr)
9
8
7
6
5
4
3
2
1
ppm
1.99
1.98
2.05
1.02
0.98
4.06
1.05
1.15
3.24
0.97
1.12
3.13
4.68

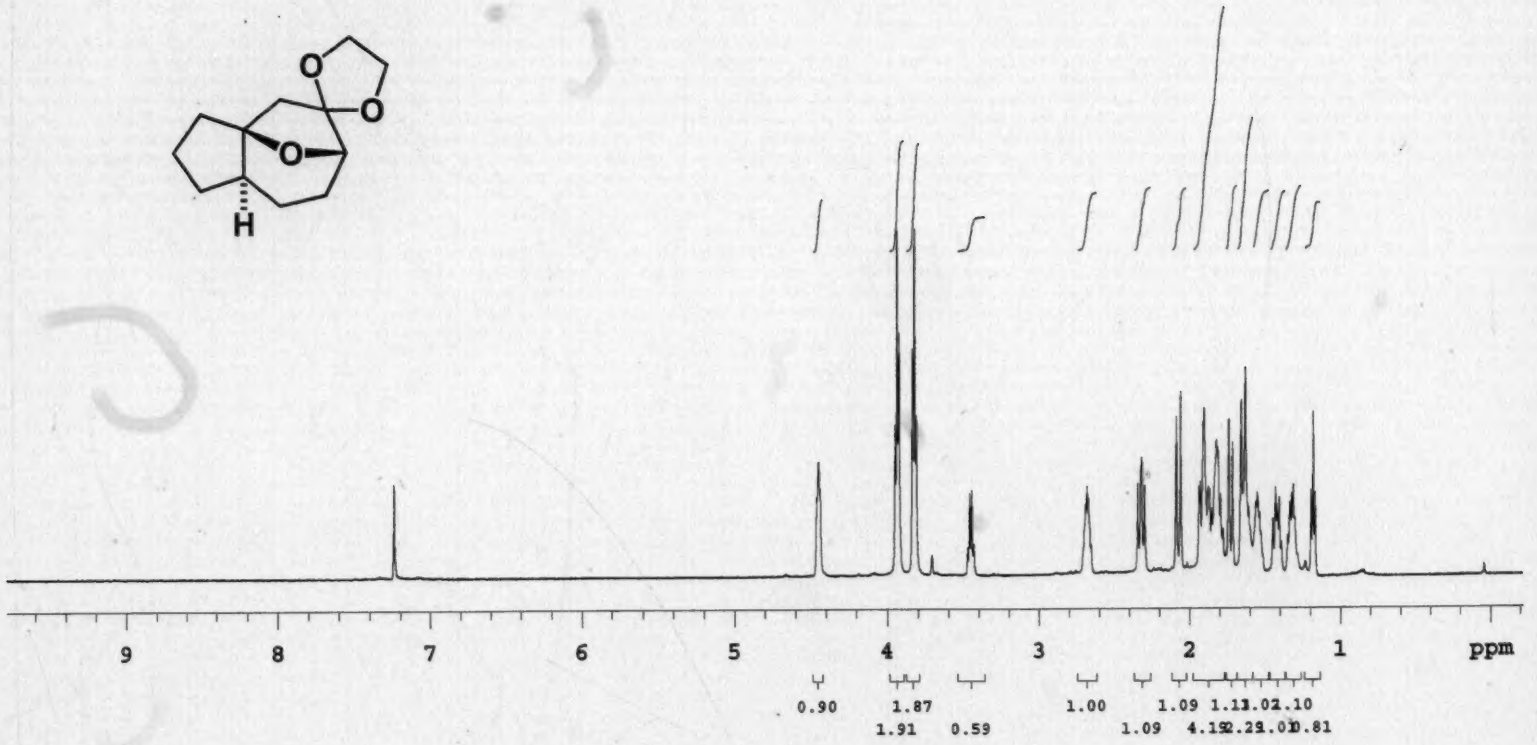

O
O
O
OEt
STol
H
(4.5 : 1 dr)
77.263
77.009
76.755
209.123
166.058
137.409
132.426
131.484
129.671
91.468
89.280
62.286
55.805
52.654
50.753
41.615
35.196
30.142
26.722
24.823
21.065
13.939
200
180
160
140
120
100
80
60
40
20
ppm

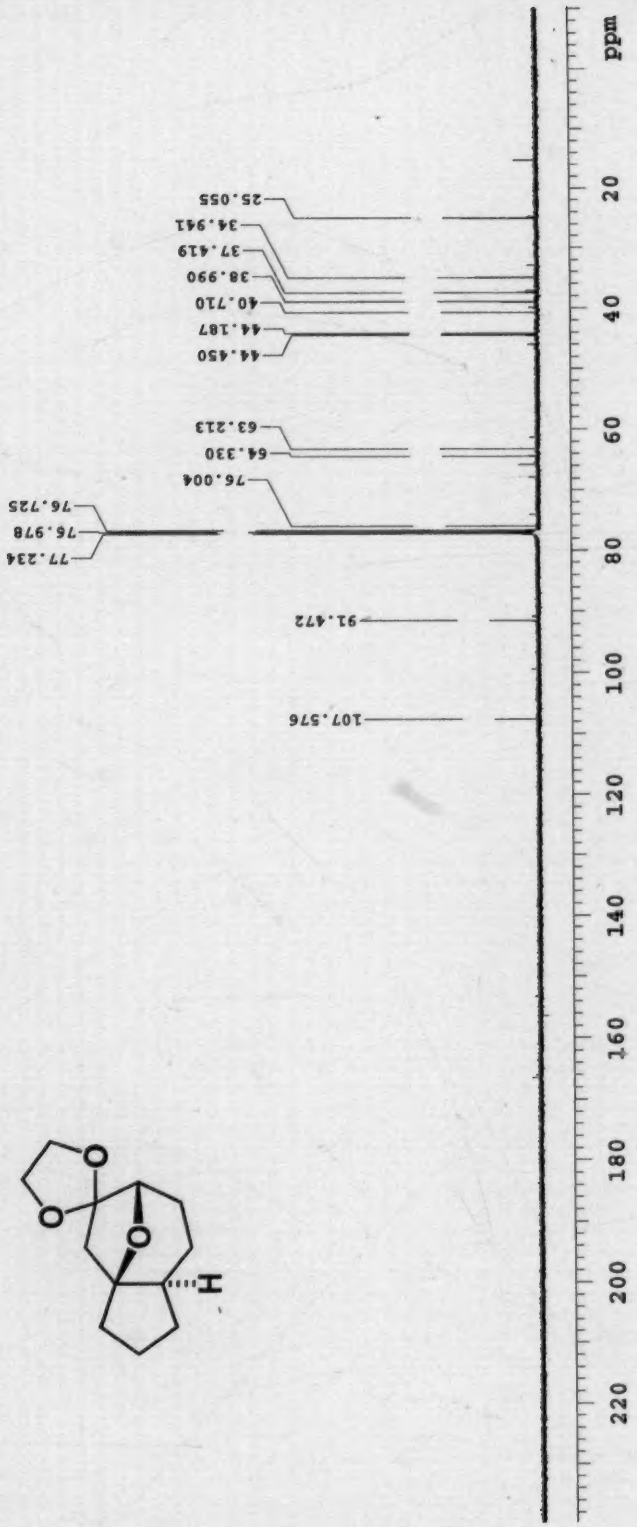

O
O
O
OEt
STol
H
9
8
7
6
5
4
3
2
1
ppm
1.85
1.94
0.98
2.04
1.06
2.21
3.18
1.08
2.80
3.46
6.00
1.35
1.08

196.299
166.784
140.239
136.293
129.714
126.411
93.908
81.205
77.245
76.737
67.353
61.567
48.309
45.285
38.566
36.684
34.381
24.919
21.317
13.968
ppm
200
180
160
140
120
100
80
60
40
20
O
O
O
OEt
STol
H

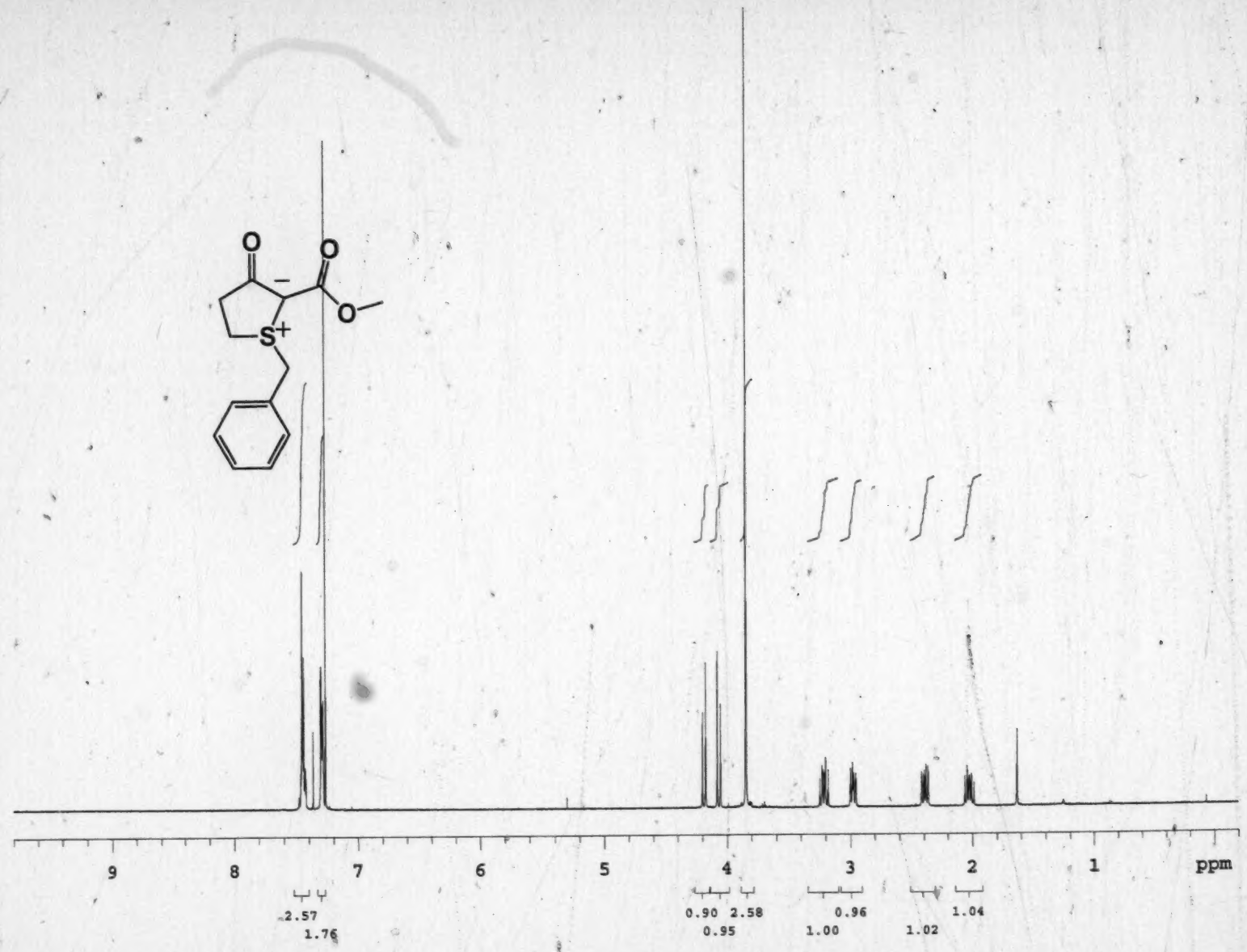

HO
O
O
H
9
8
7
6
5
4
3
2
1
ppm
1.06
1.03
1.24
4.78
1.11
2.46
2.15
2.93
3.81
3.53
2.58
2.34

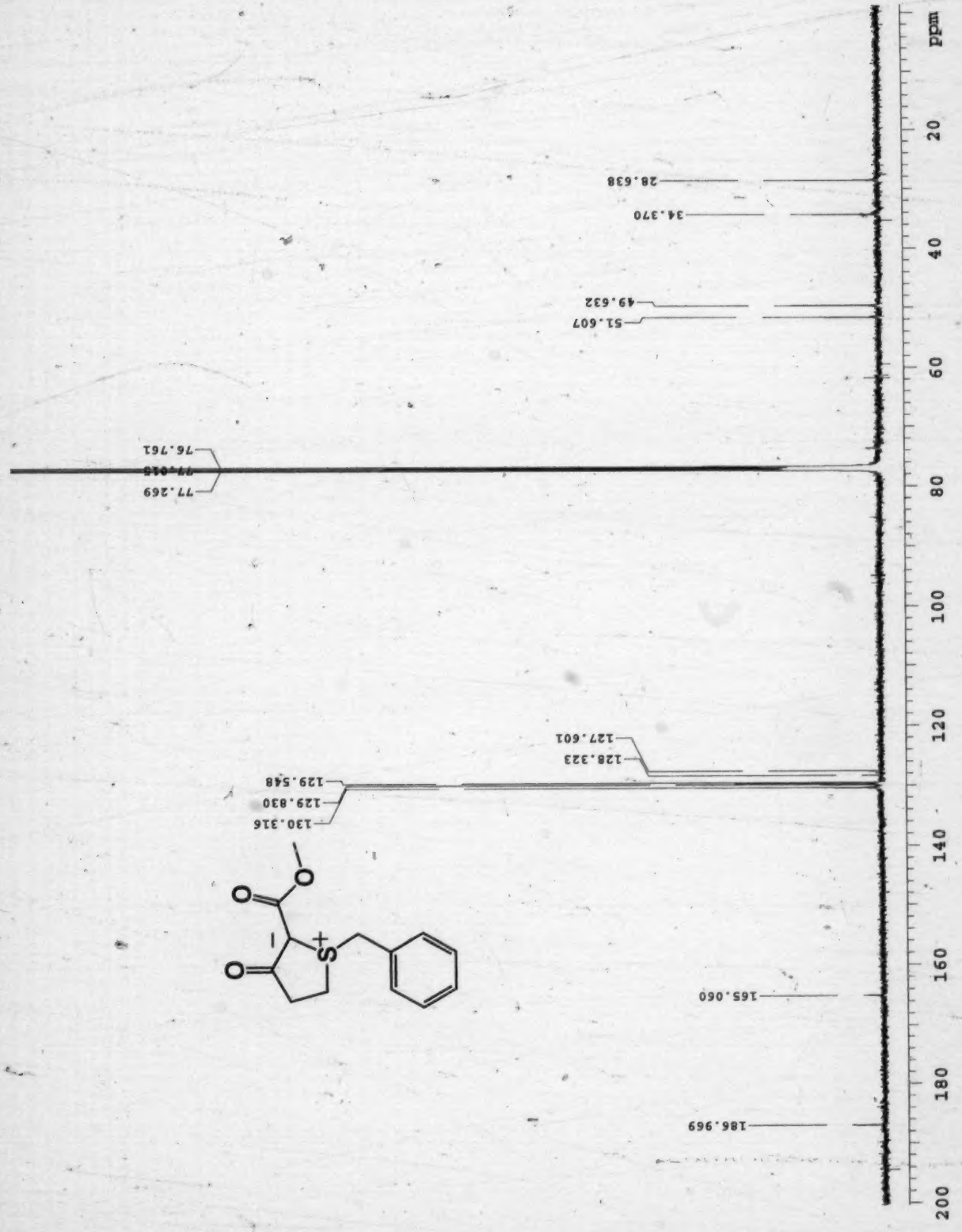

ppm
20
40
60
80
100
120
140
160
180
200
220
19.847
26.594
30.869
41.851
44.928
47.157
63.867
64.555
76.717
76.972
77.226
78.595
108.559
133.592
133.909
O
O
HO
H


O
O
O
H
9
8
7
6
5
4
3
2
1
ppm
0.90
1.87
1.91
0.59
1.00
1.09
1.09
1.11
1.02
1.10
0.81

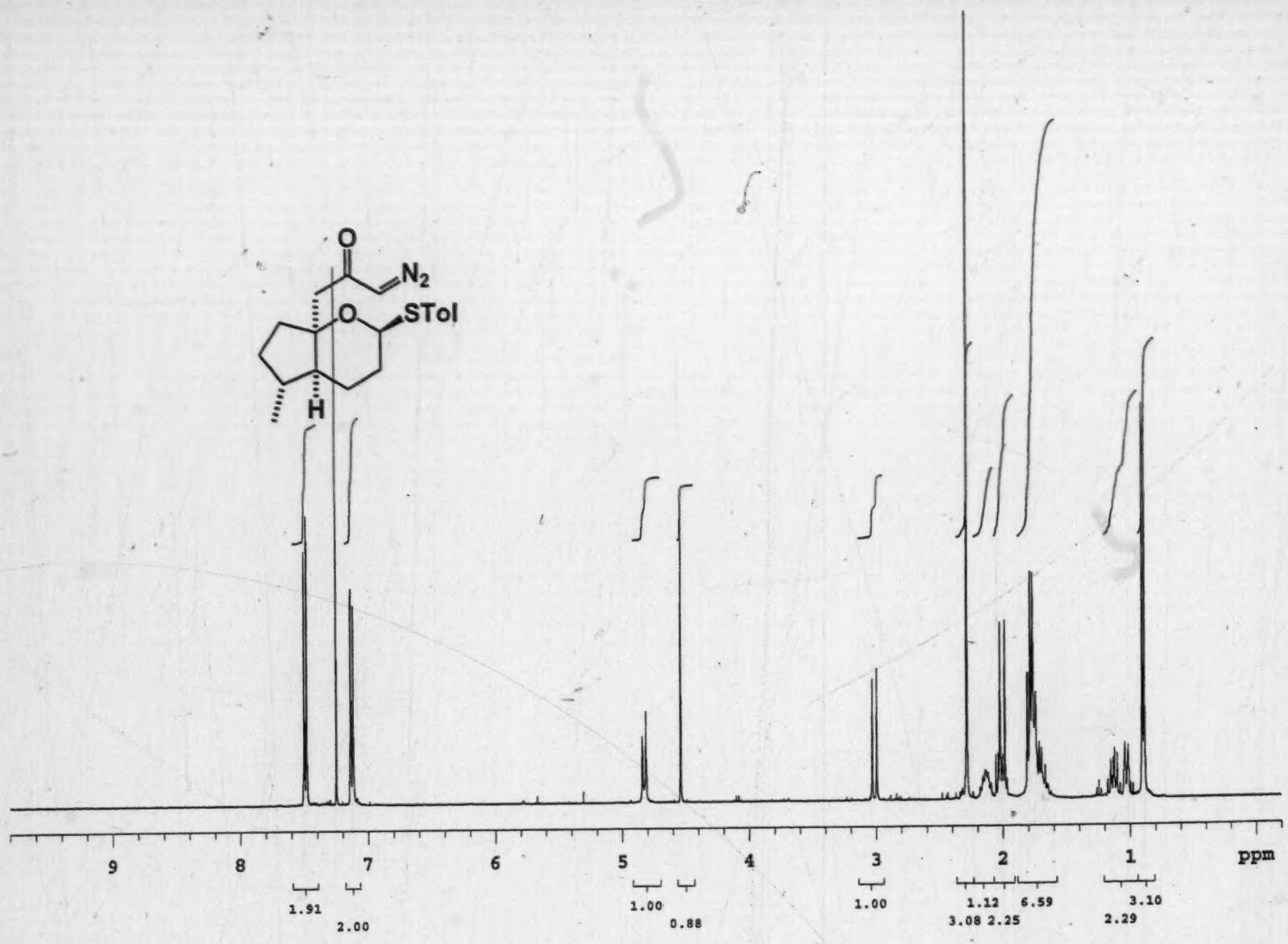

ppm
220
200
180
160
140
120
100
80
60
40
20
107.576
91.472
77.234
76.978
76.725
76.004
64.330
63.213
44.450
44.187
40.710
38.990
37.419
34.941
25.055
O
O
O
H

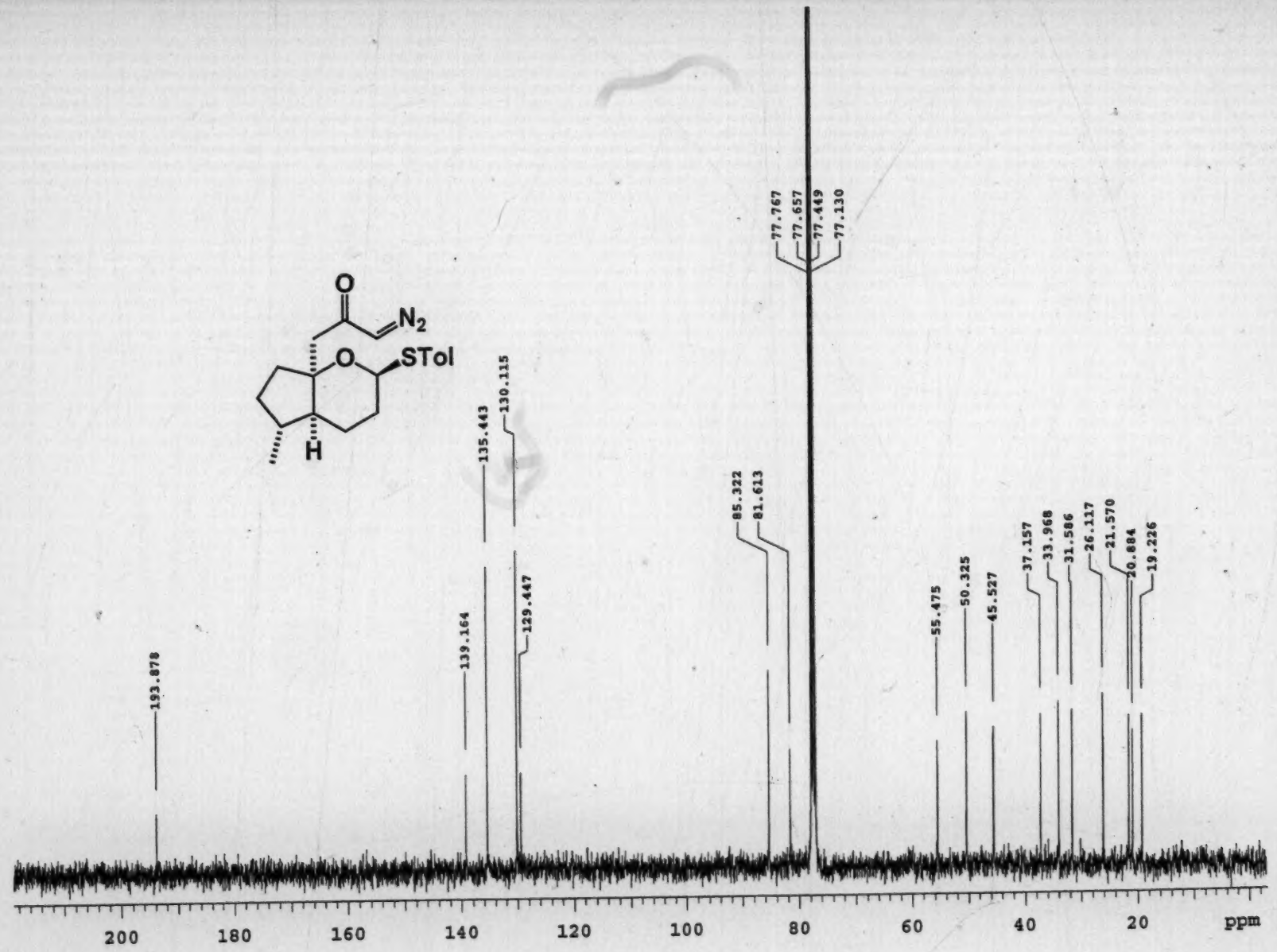
Appendix Chapter 3

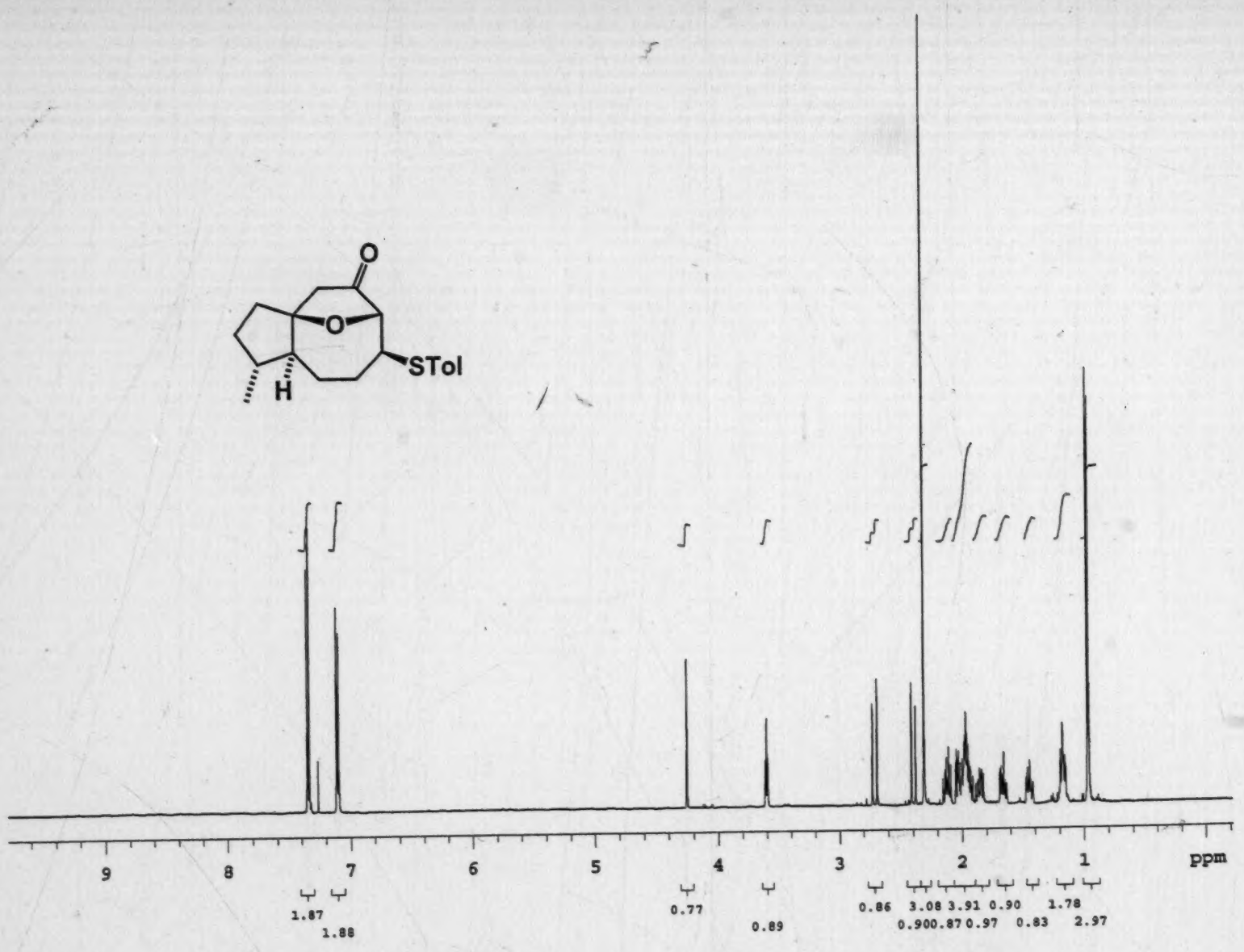

O
O
O
S+
9
8
7
6
5
4
3
2
1
ppm
2.57
1.76
0.90
2.58
0.95
1.00
0.96
1.02
1.04

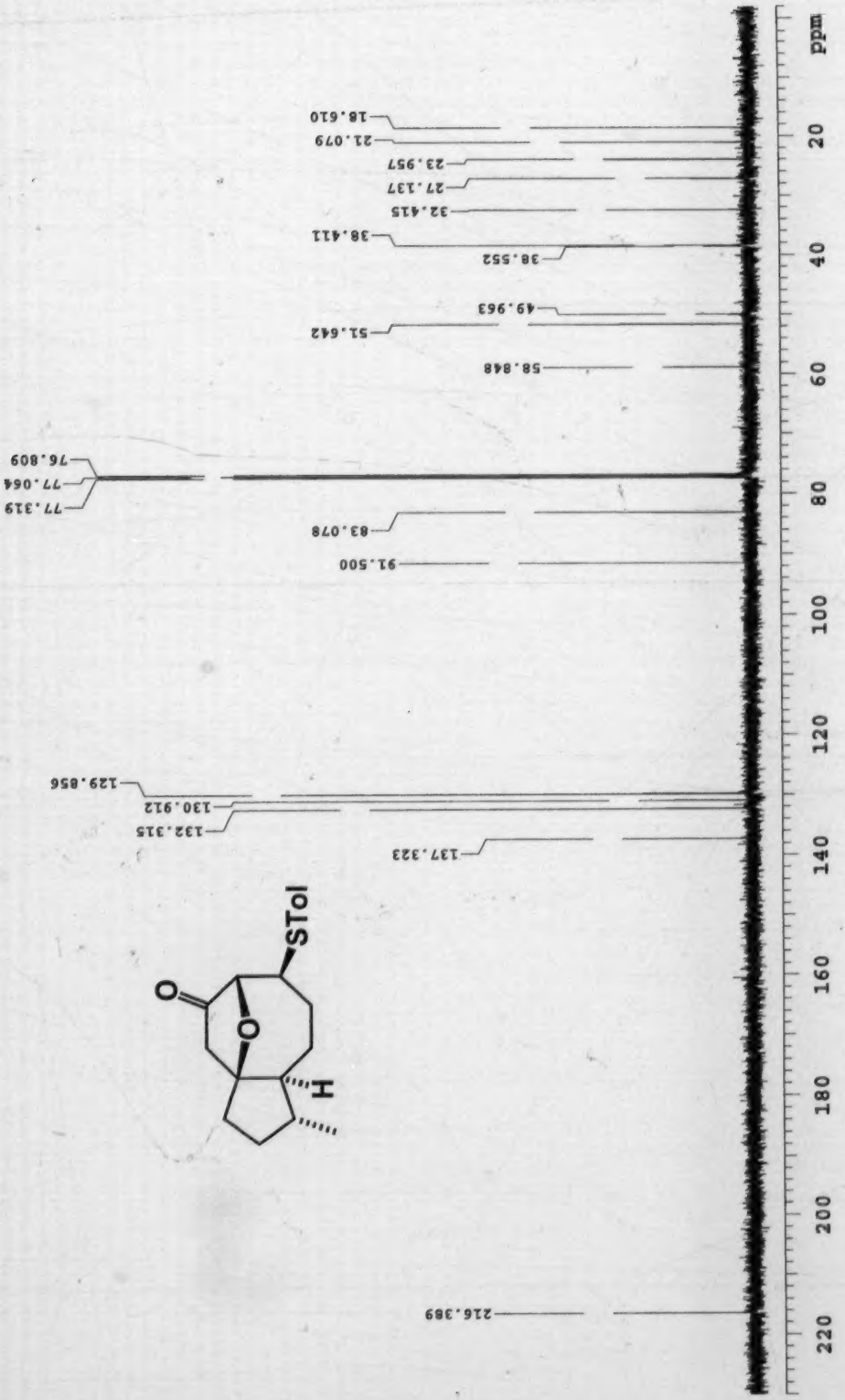

ppm
20
40
60
80
100
120
140
160
180
200
28.638
34.370
49.632
51.607
76.761
77.269
127.601
128.323
129.548
129.830
130.316
165.060
186.969
O
O
O
S

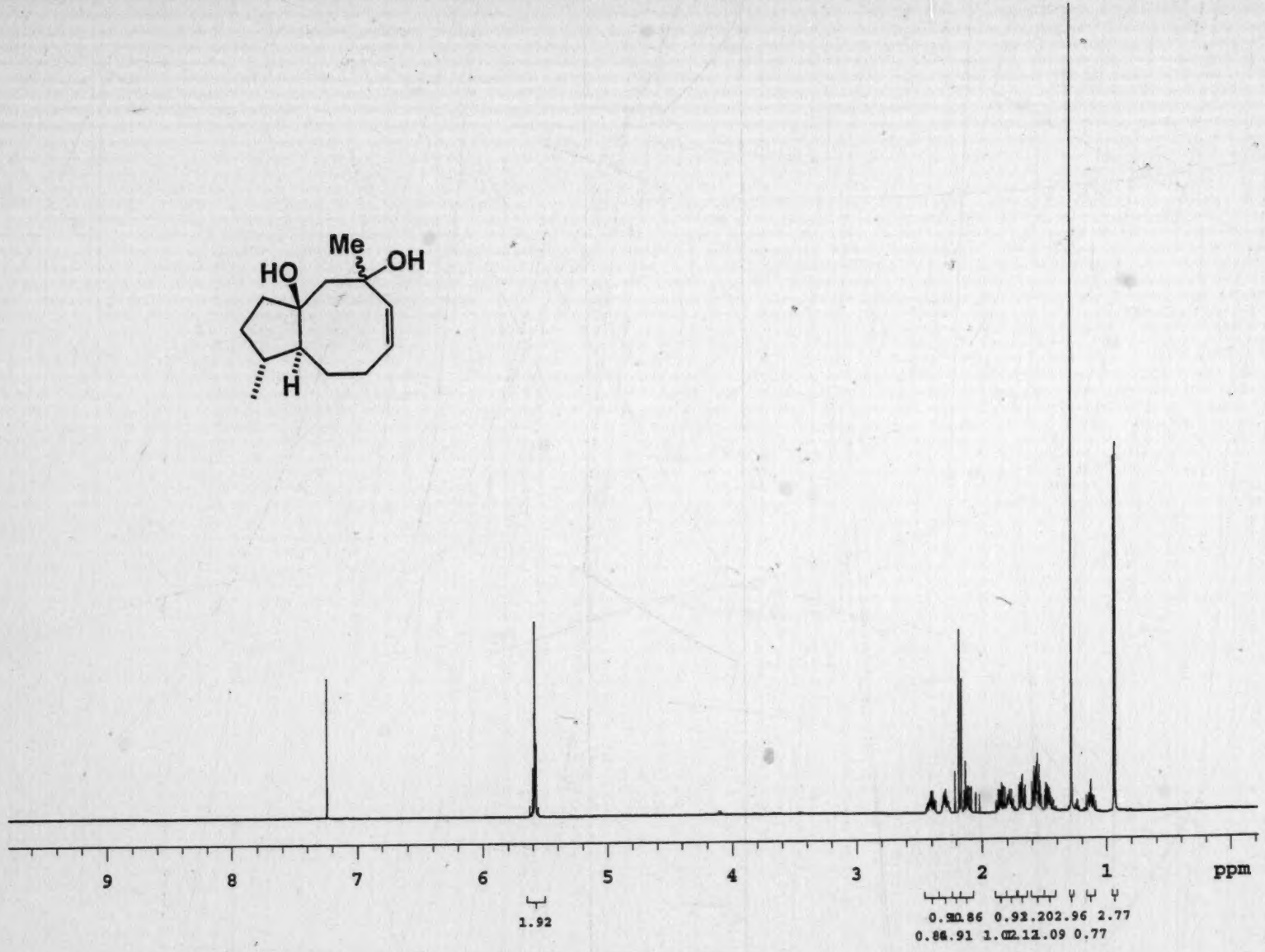
Appendix Chapter 4

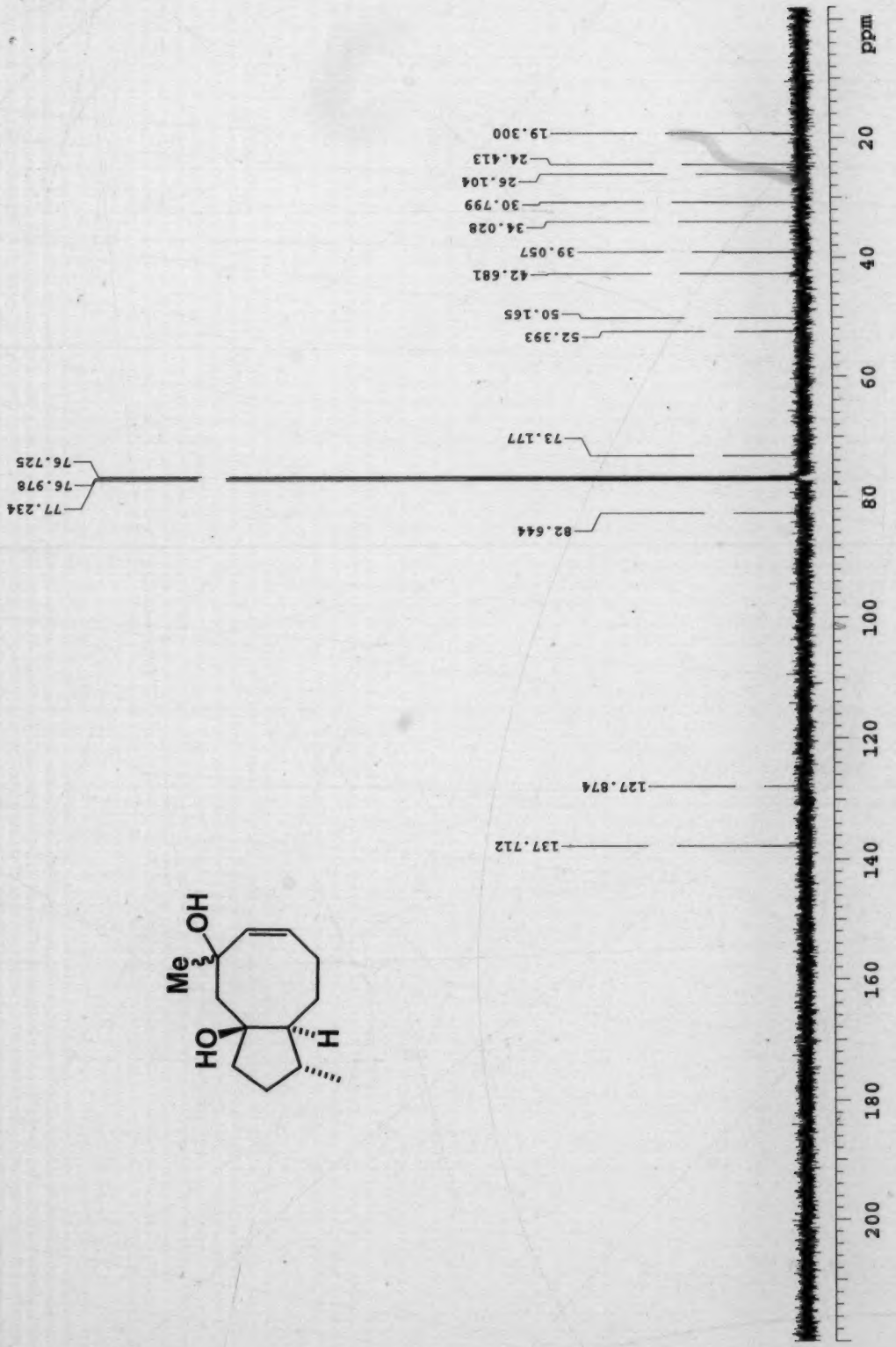

O
N2
O
STol
H
9
8
7
6
5
4
3
2
1
ppm
1.91
2.00
1.00
0.88
1.00
1.12
6.59
3.08
2.25
2.29
3.10


O
N2
O
STol
H
193.878
139.164
135.443
130.115
129.447
85.322
81.613
77.767
77.657
77.449
77.130
55.475
50.325
45.527
37.157
33.968
31.586
26.117
21.570
20.884
19.226
200
180
160
140
120
100
80
60
40
20
ppm

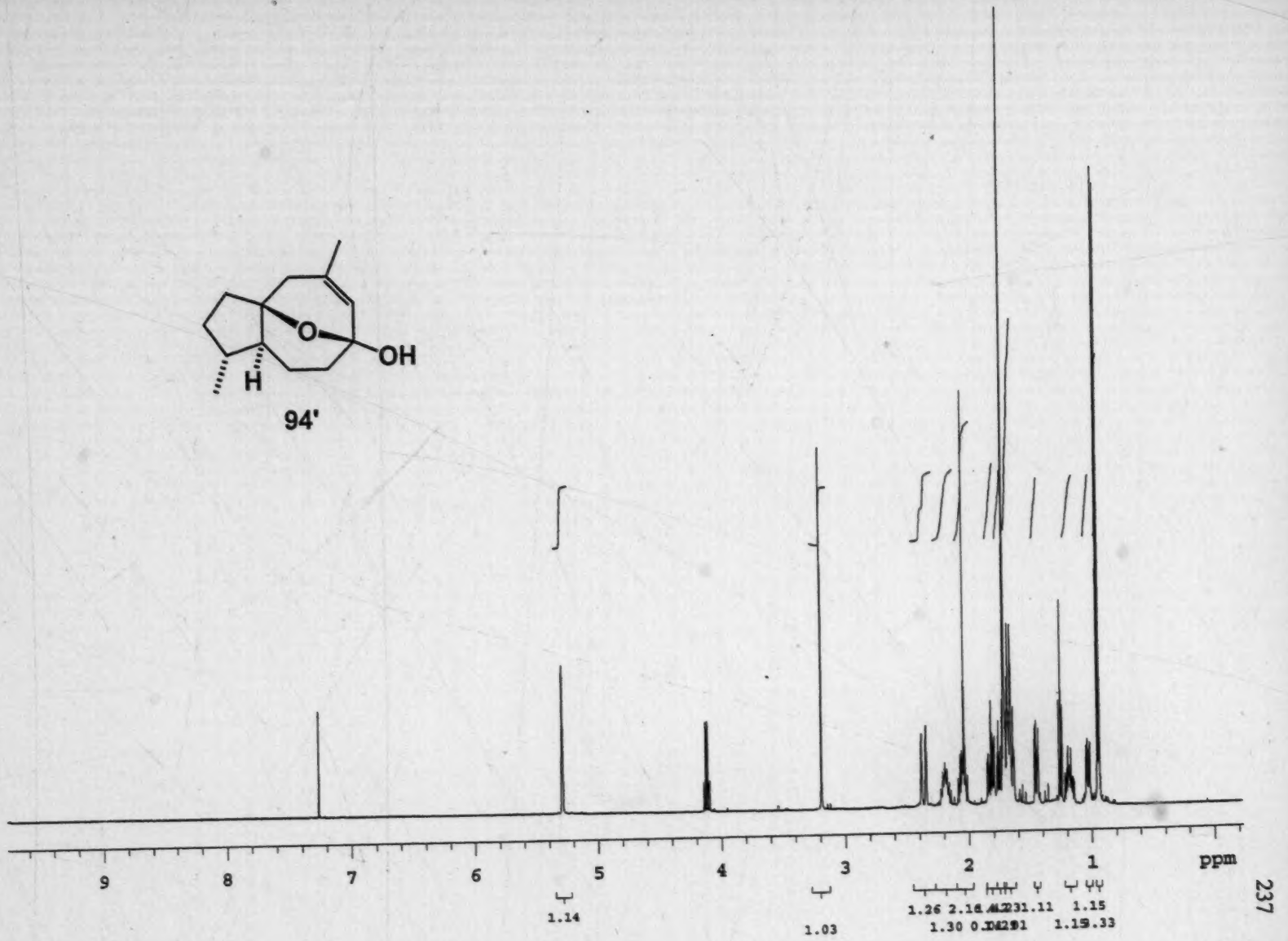

O
O
STol
H
9
8
7
6
5
4
3
2
1
ppm
1.87
1.88
0.77
0.89
0.86
3.08
3.91
0.90
1.78
0.90
0.87
0.97
0.83
2.97


216.389
137.323
132.315
130.912
129.856
91.500
83.078
77.319
77.064
76.809
58.848
51.642
49.963
38.552
38.411
32.415
27.137
23.957
21.079
18.610
ppm
20
40
60
80
100
120
140
160
180
200
220
STol
O
O
H


Me
HO
OH
H
9
8
7
6
5
4
3
2
1
ppm
1.92
0.86 0.92 2.96 2.77
0.91 1.09 0.77

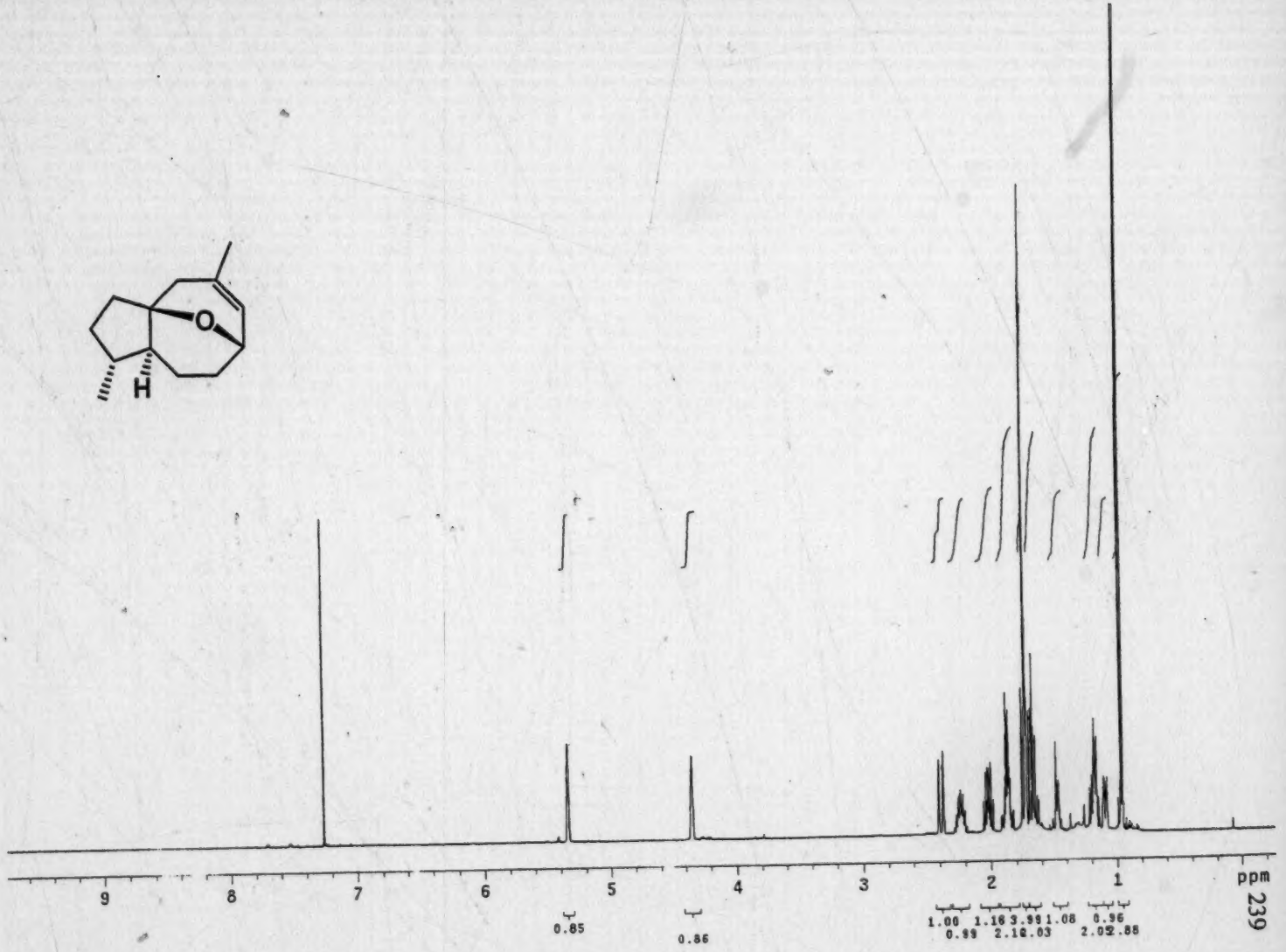

ppm
20
40
60
80
100
120
140
160
180
200
19.300
24.413
26.104
30.799
34.028
39.057
42.681
50.165
52.393
73.177
76.725
76.978
77.234
82.644
127.874
137.712
Me
OH
HO
H

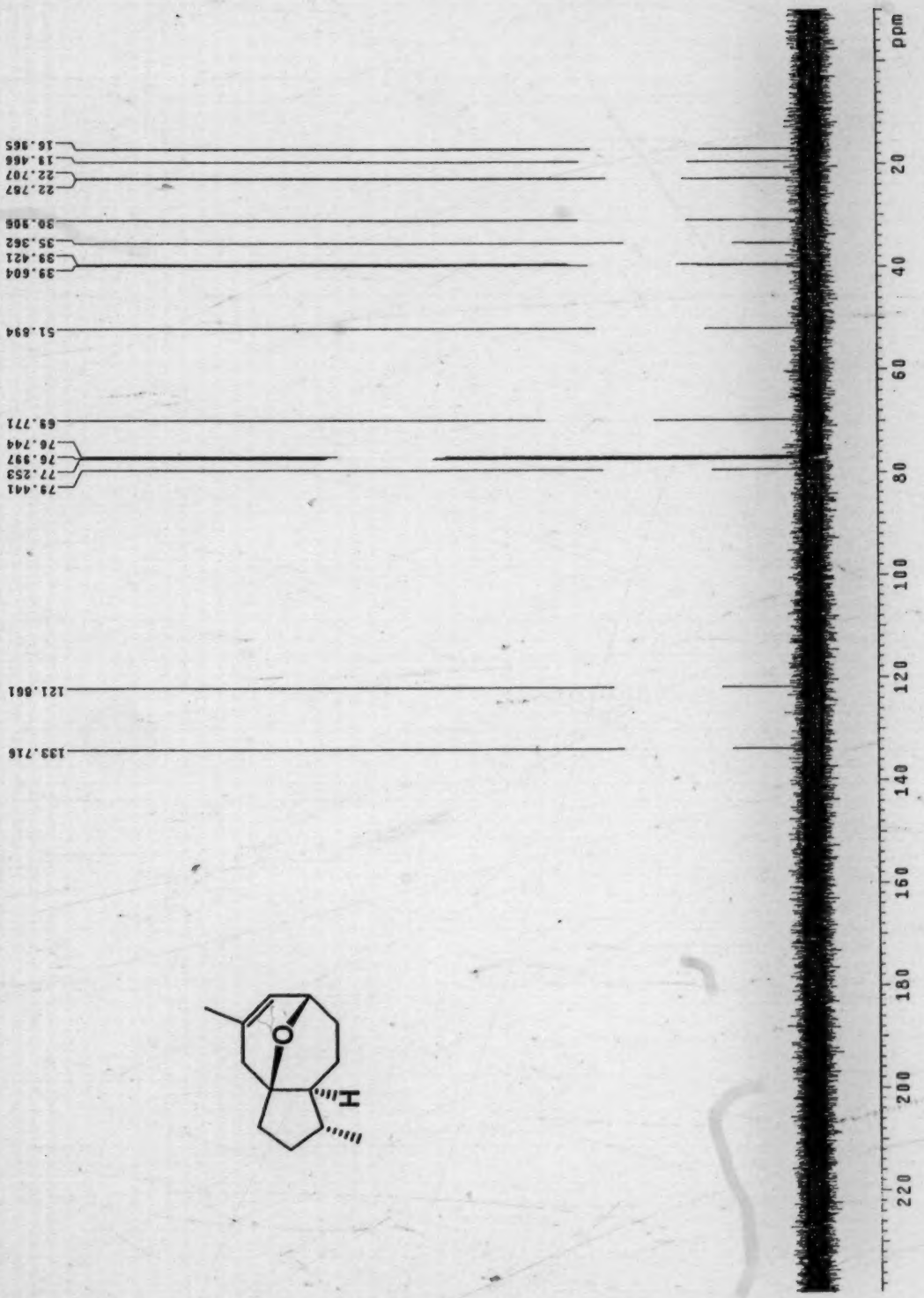
94'



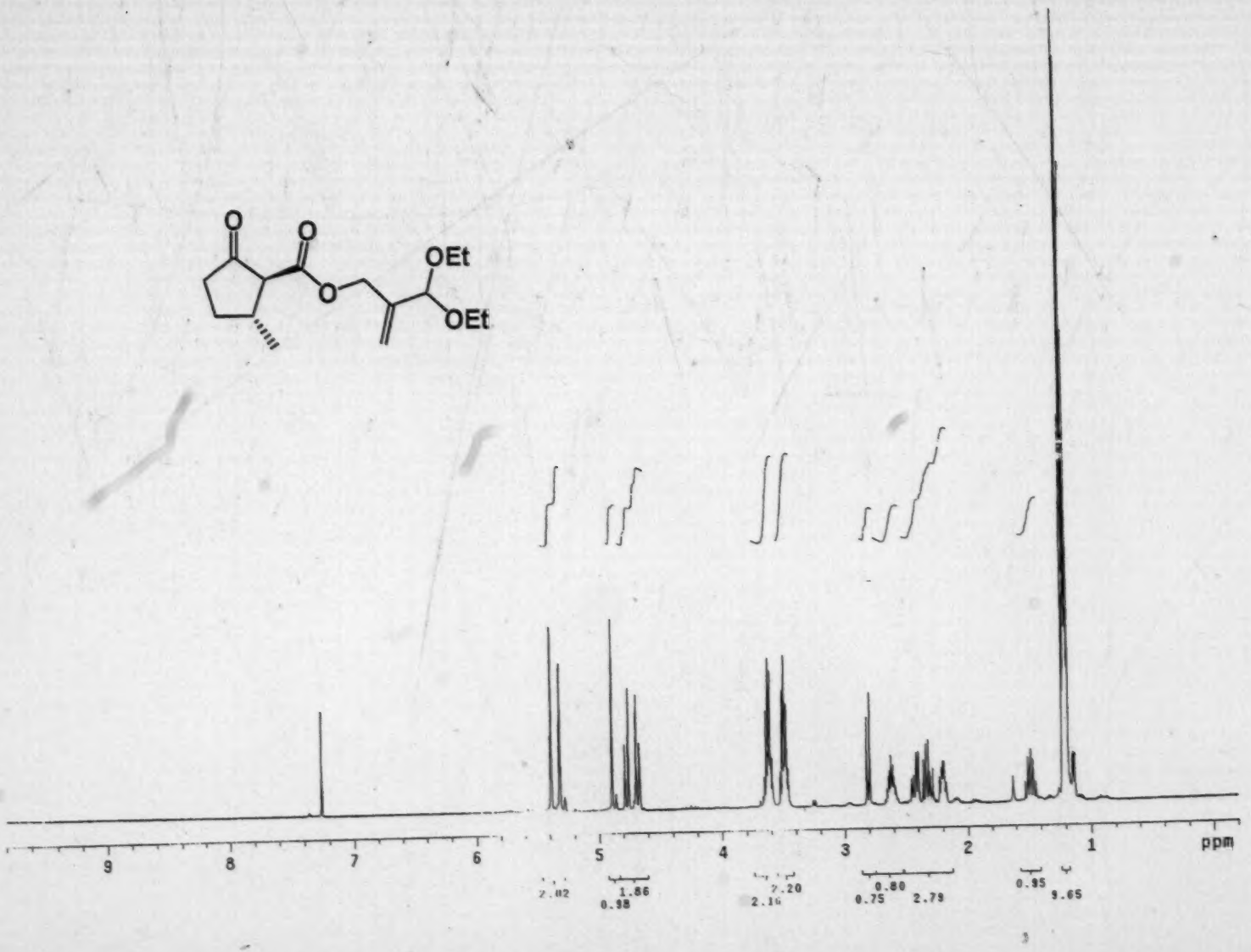
ppm
200
180
160
140
120
100
80
60
40
20
136.734
123.693
95.982
84.750
77.272
77.016
76.761
50.937
38.950
35.300
30.787
29.260
22.312
20.646
19.373
OH
O
H
94'

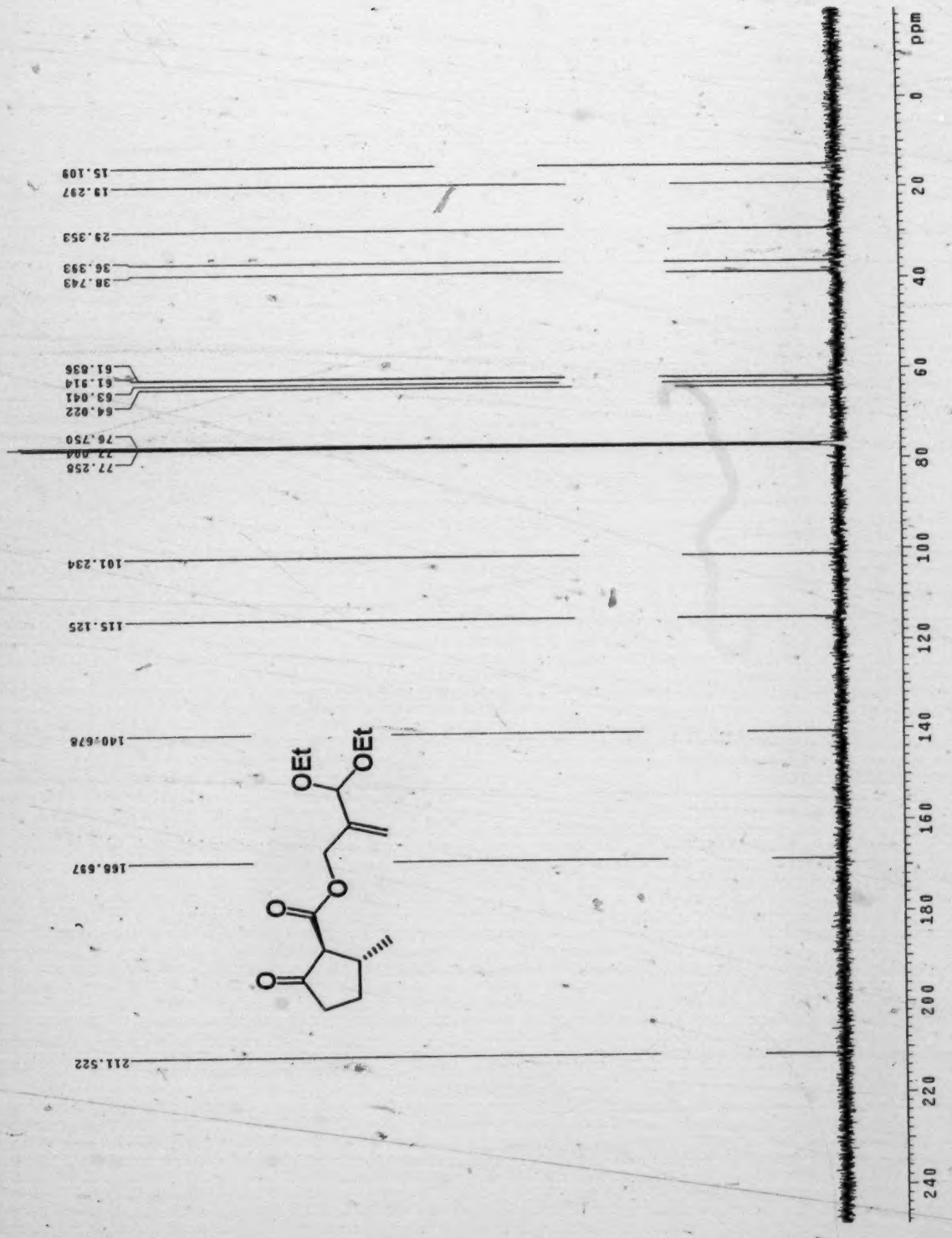
O
H

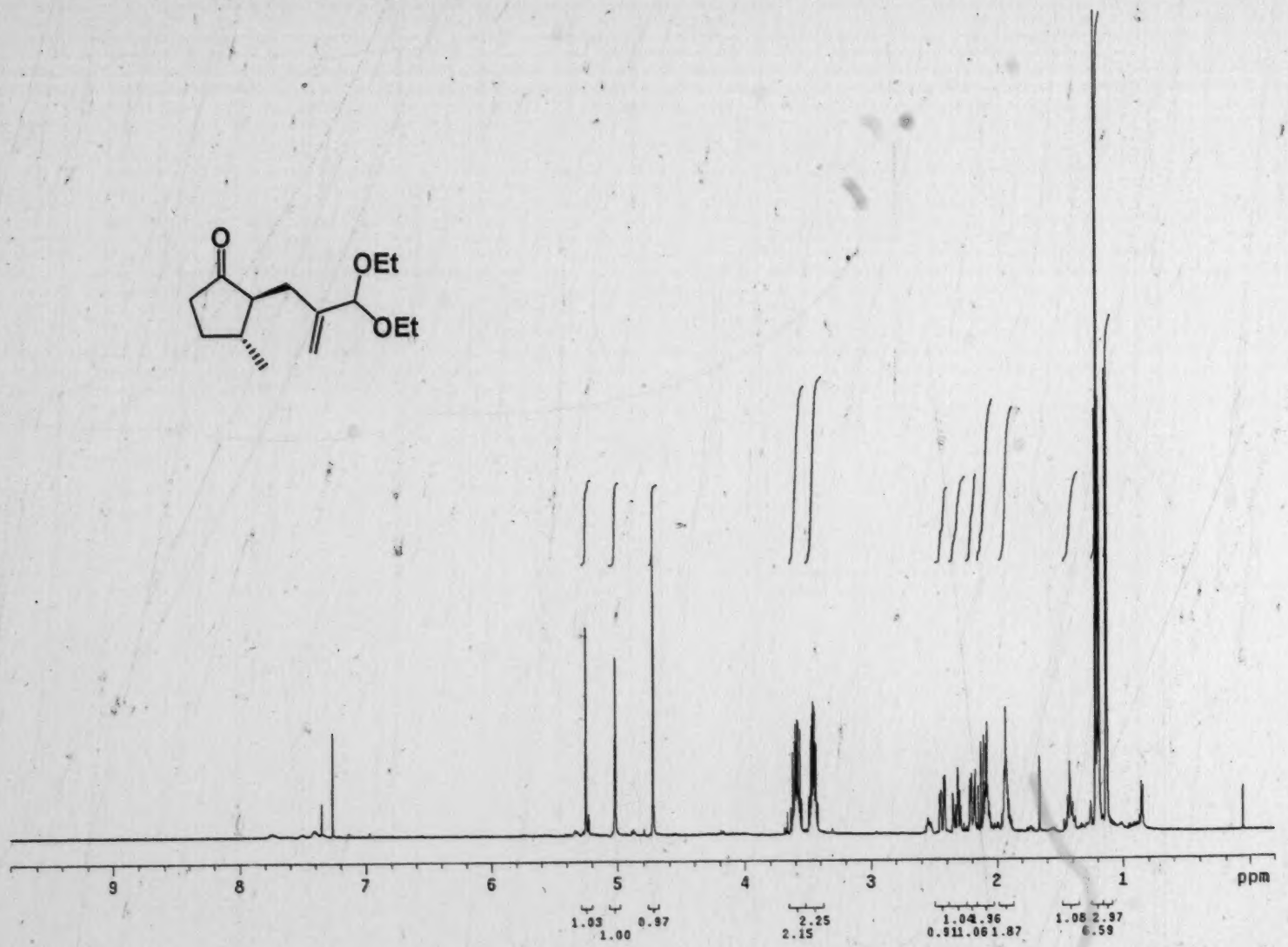

9
8
7
6
5
4
3
2
1
ppm
0.85
0.86
1.00
0.99
1.16
2.10
3.99
2.03
1.08
0.96
2.05
2.88

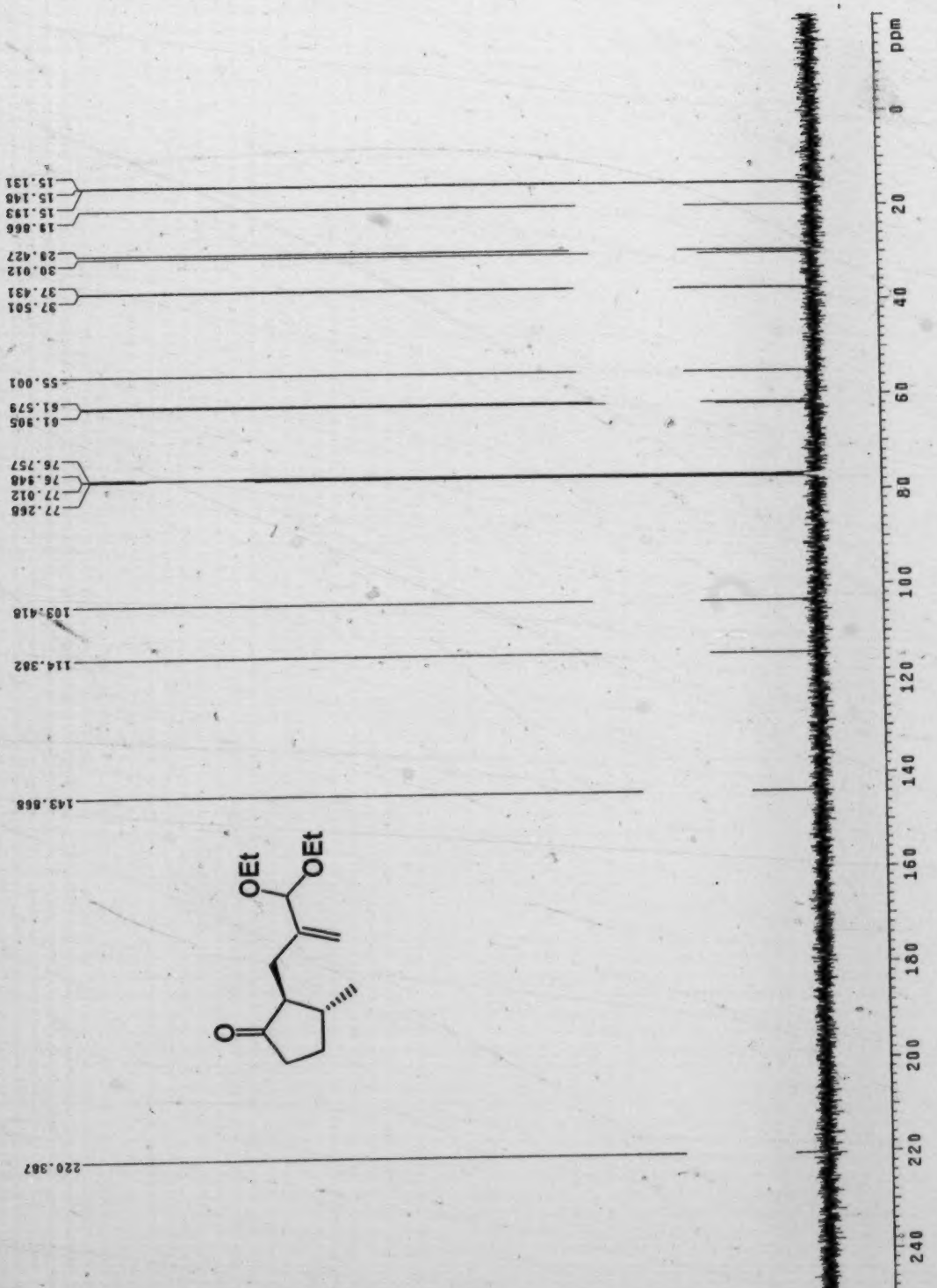

16.965
19.466
22.707
22.767
30.906
35.362
39.421
39.604
51.894
69.771
76.744
76.997
77.253
79.441
121.861
133.716
ppm
20
40
60
80
100
120
140
160
180
200
220

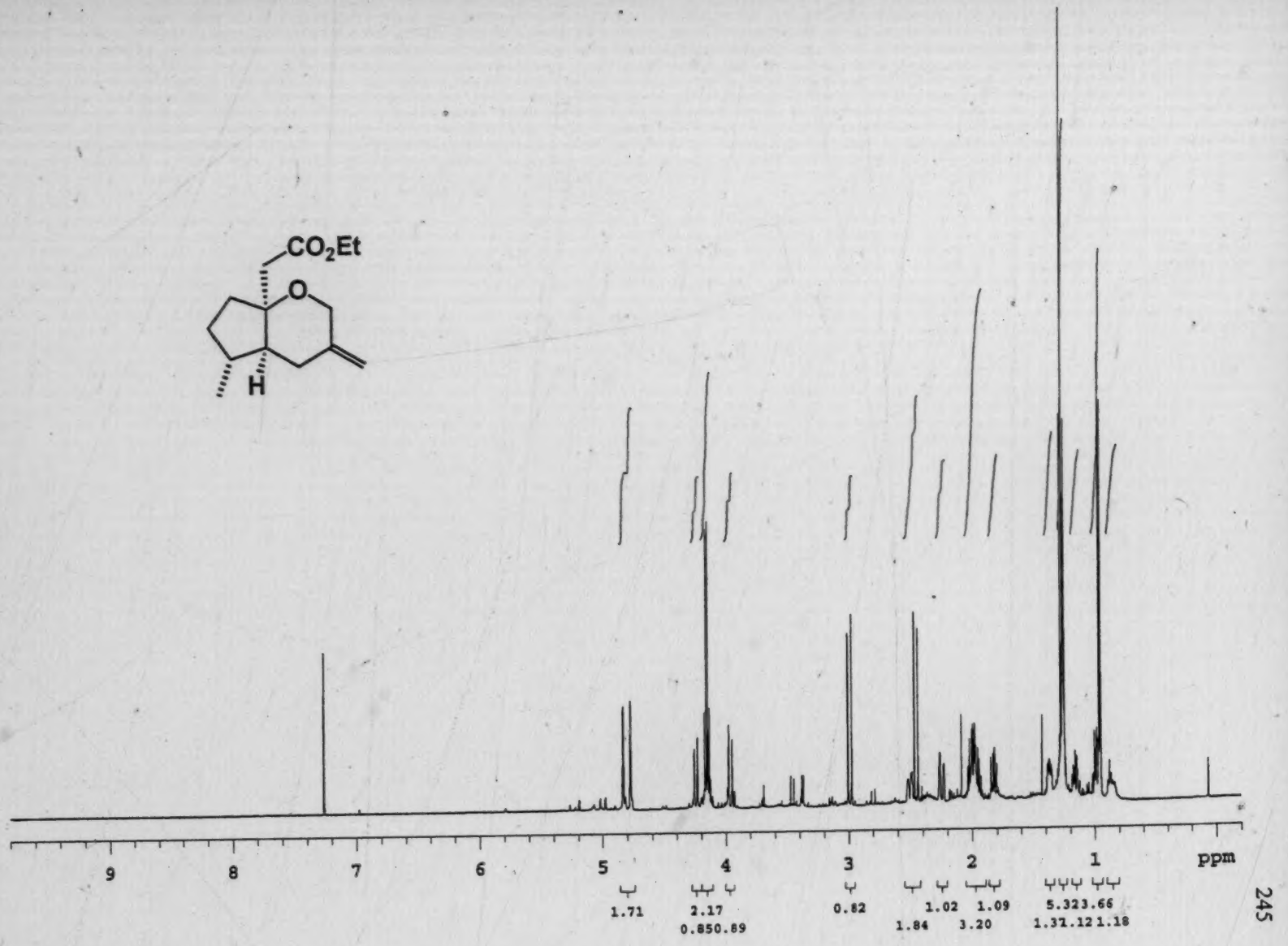
O
H

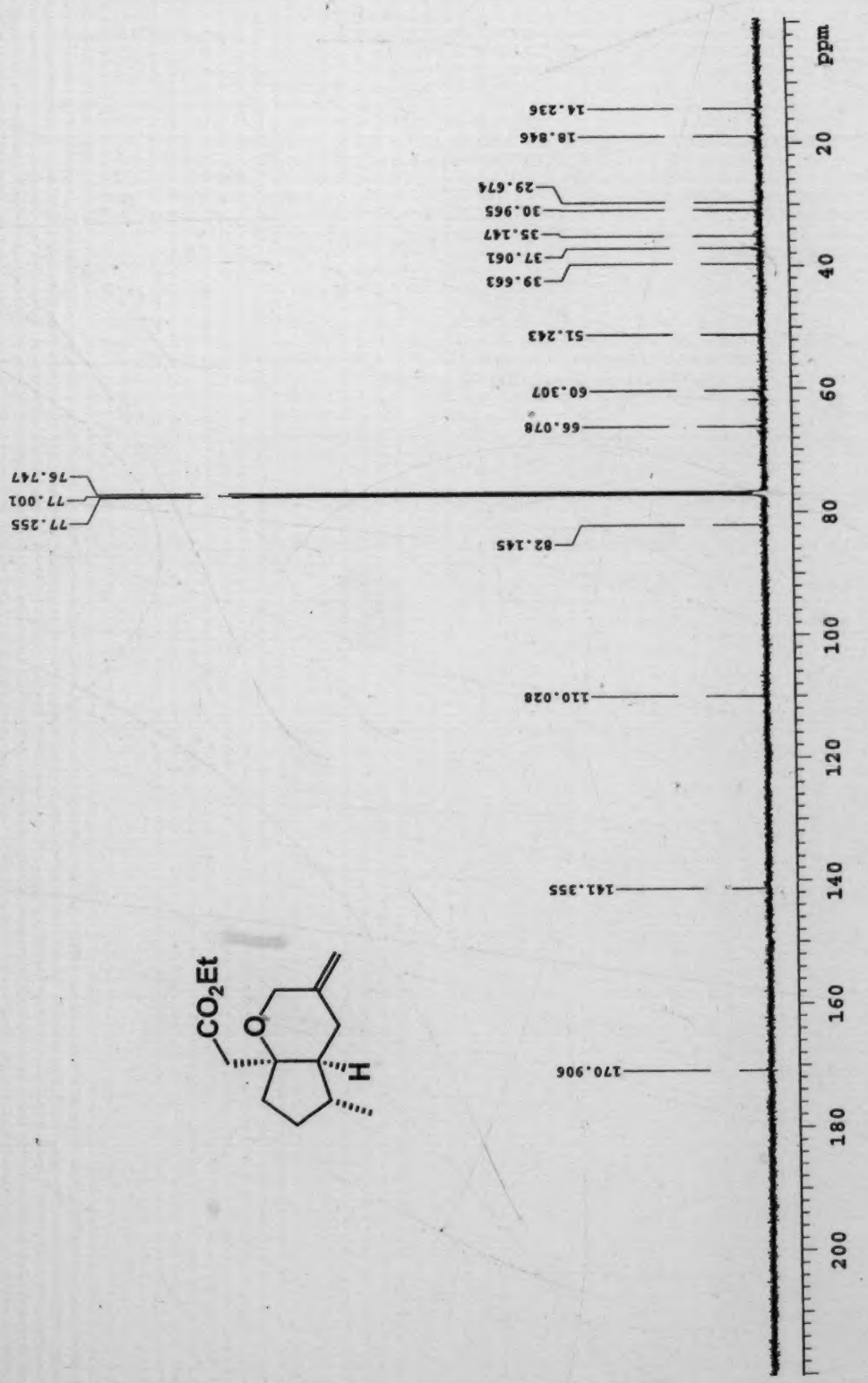

O
O
O
OEt
OEt
9
8
7
6
5
4
3
2
1
ppm
2.02
1.86
0.98
7.20
2.14
0.80
0.75
2.79
0.95
9.65


15.109
19.297
29.353
36.393
38.743
61.636
61.914
63.041
64.022
76.750
77.258
101.234
115.125
140.678
166.637
211.522
OEt
OEt
O
O
O
ppm
0
20
40
60
80
100
120
140
160
180
200
220
240


O
OEt
OEt
9
8
7
6
5
4
3
2
1
ppm
1.03
1.00
0.97
2.25
2.15
1.04
0.91
1.96
1.06
1.87
1.08
2.97
6.59


15.131
15.148
15.193
19.866
29.427
30.012
37.431
37.501
55.001
61.579
61.905
76.757
76.948
77.012
77.268
103.418
114.382
143.868
220.367
OEt
OEt
O
ppm
0
20
40
60
80
100
120
140
160
180
200
220
240


CO2Et
O
H
9
8
7
6
5
4
3
2
1
ppm
1.71
2.17
0.85
0.89
0.82
1.84
1.02
3.20
1.09
5.32
1.37
3.66
1.12
1.18


ppm
20
40
60
80
100
120
140
160
180
200
14.236
18.846
29.674
30.965
35.147
37.061
39.663
51.243
60.307
66.078
77.255
77.001
76.747
82.145
110.028
141.355
170.906
CO2Et
O
H